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(54) Title: NUCLEIC ACIDS, PROTEINS, AND ANTIBODIES

(57) Abstract: The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Nucleic Acids, Proteins, and Antibodies

This application refers to a "Sequence Listing" that is provided on electronic media in computer readable form pursuant to Administrative Instructions Section 801(a)(i) and as a paper copy. The Sequence Listing forms a part of this description pursuant to Rule 5.2 and Administrative Instructions Sections 801 to 806, and is hereby incorporated in its entirety.

The Sequence Listing is provided as an electronic file (PA131PCTSL..txt, 5,210,863 bytes in size, created on May 18, 2001) on three identical compact discs (CD-R), labeled "COPY 1," "COPY 2," and "CRF." The Sequence Listing complies with Annex C of the Administrative Instructions, and may be viewed, for example, on an IBM-PC machine running the MS-Windows operating system by using the V viewer software, version 2000 (see World Wide Web URL: http://www.fileviewer.com).

Field of the Invention

[0001] The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Background of the Invention

[0002] Protein transport is a quintessential process for both prokaryotic and eukaryotic cells. Transport of an individual protein usually occurs via an amino-terminal signal sequence, which directs, or targets, the protein from its ribosomal assembly site to a particular cellular or extracellular location. Transport may involve any combination of several of the following steps: contact with a chaperone, unfolding, interaction with a receptor and/or a pore complex, addition of energy, and refolding. Moreover, an

extracellular protein may be produced as an inactive precursor. Once the precursor has been exported, removal of the signal sequence by a signal peptidase activates the protein.

[0003] Although amino-terminal signal sequences vary substantially, many patterns and overall properties are shared. Recently, hidden Markov models (HMMs), statistical alternatives to FASTA and Smith Waterman algorithms, have been used to find shared patterns, specifically consensus sequences (Pearson, W.R. and D.J. Lipman PNAS 85:2444-48 (1988); Smith, T.F. and M.S. Waterman J. Mol. Biol. 147:195-97 (1981)). Although they were initially developed to examine speech recognition patterns, HMMs have been used in biology to analyze protein and DNA sequences and to model protein structure (Krogh, A. et al. J. Mol. Biol. 235:1501-31 (1994); Collin, M. et al. Protein Sci. 2:305-14 (1993)). HMMs have a formal probabilistic basis and use position-specific scores for amino acids or nucleotides and for opening and extending an insertion or deletion. The algorithms are quite flexible in that they incorporate information from newly identified sequences to build even more successful patterns. Other methods exist to identify membrane associated proteins. Klein et al. have developed a method ("ALOM", also called as KKD) to detect potential transmembrane segments in polypeptides (Klein, P. et al. Biochim. Biophys. Acta, 815:468 (1985)). It attempts to identify the most probable transmembrane segment from the average hydrophobicity value over a range of amino acid residues. It predicts whether the segment is a transmembrane segment (INTEGRAL) or not (PERIPHERAL) and thus, can suggest membrane association of a polypeptide.

[0004] Some examples of the protein families which are known to be plasma membrane associated are receptors (nuclear, 4 transmembrane, G protein coupled, and tyrosine kinase), cytokines (chemokines), hormones (growth and differentiation factors), neuropeptides and vasomediators, protein kinases, phosphatases, phospholipases, phosphodiesterases, nucleotide cyclases, matrix molecules (adhesion, cadherin, extracellular matrix molecules, integrin, and selectin), seven transmembrane receptors, ion channels (calcium, chloride, potassium, and sodium), proteases, transporter/pumps (amino acid, protein, sugar, metal and vitamin; calcium, phosphate, potassium, and sodium) and regulatory proteins. Descriptions of some of these proteins (seven transmembrane receptors, kinases, matrix proteins, fibronectins, defensins, EF-hand domain containing

proteins, mac/perforin family members, pancreatic hormones, serine carboxypeptidases, tumor necrosis factors (TNFs)) and diseases associated with their dysfunction follow.

Seven transmembrane receptors-

[0005] The seven transmembrane receptors (also known as heptahelical, serpentine, or G protein-coupled receptors) comprise a superfamily of structurally related molecules. Possible relationships among seven transmembrane receptors (7TM receptors) for which amino acid sequence had previously been reported are reviewed in Probst et al., DNA and Cell Biology, 11(1):1-20 (1992). Briefly, the 7TM receptors exhibit detectable amino acid sequence similarity and all appear to share a number of structural characteristics including: an extracellular amino terminus; seven predominantly hydrophobic α -helical domains (of about 20-30 amino acids) which are believed to span the cell membrane and are referred to as transmembrane domains TM 1-7; approximately twenty well-conserved amino acids; and a cytoplasmic carboxy terminus.

[0006] Each 7TM receptor is predicted to associate with a particular G protein at the intracellular surface of the plasma membrane. The binding of the receptor to its ligand is thought to result in activation (i.e., the exchange of GTP for GDP on the α -subunit) of the G protein which in turn stimulates specific intracellular signal-transducing enzymes and channels. Thus, the function of each 7TM receptor is to discriminate its specific ligand from the complex extracellular milieu and then to activate G proteins to produce a specific intracellular signal. Transmembrane domain-3 (TM3) is believed to be essential in signal transduction (Cotecchia et al., *Proc. Natl. Acad. Sci.*, USA, 87:2896-2900 (1990)). Other regions may be essential for biological activity as well (Lefkowitz, *Nature*, 265:603-604 (1993)).

[0007] Mutations in the third intracellular loop of one 7TM receptor (the thyrotropin receptor) and in the adjacent sixth transmembrane domain of another 7TM receptor (the luteinizing hormone receptor) have been reported to be the genetic defects responsible for an uncommon form of hyperthyroidism (Parma et al., Nature, 365:649-651 (1993) and for familial precocious puberty (Shenker et al., Nature, 365:652-654 (1993)), respectively. In both cases the mutations result in constitutive activation of the G protein receptors. Other studies have shown that mutations that prevent the activation of 7TM receptors are responsible for states of hormone resistance which are responsible for diseases such as

congenital nephrogenic diabetes insipidus. See Rosenthal et al., *J. Biol. Chem.*, 268:13030-13033 (1993). Still other studies have shown that several 7TM receptors can function as protooncogenes and be activated by mutational alteration. See, for example, Allen et al., *Proc. Natl. Acad. Sci. USA*, 88:11354-11358 (1991) which suggests that spontaneously occurring mutations in some 7TM receptors may alter the normal function of the receptors and result in uncontrolled cell growth associated with human disease states such as neoplasia and atherosclerosis. Therefore, mutations in 7TM receptors may underlie a number of human pathologies.

Kinases-

[0008] The kinases comprise the largest known group of proteins, a superfamily of enzymes with widely varied firmtions and specificities. Kinases regulate many different cell proliferation, differentiation, and signaling processes by adding phosphate groups to proteins. Receptor mediated extracellular events trigger the transfer of these high energy phosphate groups and activate intracellular signaling cascades. Activation is roughly analogous to the turning on a molecular switch, and in cases where signalling is uncontrolled, may be associated with or produce inflammation and cancer.

[0009] Almost all kinases contain a similar 250-300 amino acid catalytic domain. The N-terminal domain, which contains subdomains I-IV, generally folds into a two-lobed structure which binds and orients the ATP (or GTP) donor molecule. The larger C terminal lobe, which contains subdomains VIA-XI, binds the protein substrate and carries out the transfer of the gamma phosphate from ATP to the hydroxyl group of a serine, threonine, or tyrosine residue. Subdomain V spans the two lobes.

[0010] The kinases may be categorized into families by the different amino acid sequences (between 5 and 100 residues) located on either side of, or inserted into loops of, the kinase domain. These amino acid sequences allow the regulation of each kinase as it recognizes and interacts with its target protein. The primary structure of the kinase domain is conserved and contains specific residues and identifiable motifs or patterns of amino acids. The serine threonine kinases represent one family which preferentially phosphorylates serine or threonine residues. Many serine threonine kinases, including those from human, rabbit, rat, mouse, and chicken cells and tissues, have been described

(Hardie, G. and Hanks, S. (1995) The Protein Kinase Facts Books, Vol 1:7-20 Academic Press, San Diego, CA).

Matrix Proteins-

[0011] The matrix proteins (MPs) provide structural support, cell and tissue identity, and autocrine, paracrine and juxtacrine properties for most eukaryotic cells (McGowan, S.E. (1992) FASEB J. 6:2895-2904). MPs include adhesion molecules, integrins and selectins, cadherins, lectins, lipocalins, and extracellular matrix proteins (ECMs). MPs possess many different domains which interact with soluble, extracellular molecules. These domains include collagen-like domains, EGF-like domains, immunoglobulin-like domains, fibronectin-like domains, type A domain of von Willebrand factor (vWFA)-like modules, ankyrin repeat modules, RDG or RDG-like sequences, carbohydrate-binding domains, and calcium-binding domains.

[0012] The diversity, distribution and biochemistry of MPs is indicative of their many, overlapping roles in cell proliferation and cell signaling. MPs function in the formation, growth, remodeling, and maintenance of bone, and in the mediation and regulation of inflammation. Biochemical changes that result from congenital, epigenetic, or infectious diseases affect the expression and balance of MPs. This balance, in turn, affects the activation, proliferation, differentiation, and migration of leukocytes and determines whether the immune response is appropriate or self-destructive (Roman, J. (1996) Immunol. Res. 15:163-178).

Fibronectins-

[0013] Fibronectin proteins play a vital role in the structure and function of the extracellular matrix (ECM). Defects in the function of the ECM are thought to be involved in diseases such as osteoporosis, atherosclerosis, arthritis, and fibrotic diseases. Fibronectin enables cells to adhere to the ECM, and influences the growth and migration of cells as well as the organization of the cytoskeleton. As a major component of the ECM, Fibronectin is thought to influence such processes as cellular adhesion and migration, particularly during development, as well as processes such as wound repair (R.O. Hynes, *PNAS*, 96:2588-90 (1999)).

[0014] Fibronectin is a disulfide-linked dimeric glycoprotein composed of type I, type II, and type III fibronectin repeats. Type I repeats are approximately 45 amino acids in length and are located at the amino- and carboxy-termini of the protein. Type II domains are approximately 40-60 amino acids in length, and contain four conserved cysteines involved in disulfide bonding. It is thought that the type II domains may function in collagen binding. There are approximately 15-17 type III domains, arranged in tandem in the middle of the protein, that are thought to provide elasticity to fibronectin.

Defensins-

[0015] Mammalian defensins are produced by the epidermis and mucosal epithelium as innate effector molecules thought to function in an antimicrobial capacity. Defensins are cytotoxic peptides with a broad range of activity on gram-positive and negative bacteria, fungi, parasites, viruses, and mycobacteria. The two characterized defensins are the alpha and beta defensins. The alpha-defensins are produced by neutrophils and macrophage, while the beta-defensins are produced by epithelia (Singh, P.K., et al., *PNAS*, 95:14961-66 (1998); Lillard, J.W., et al., *PNAS*, 96:651-56 (1999)).

[0016] Defensin peptides range in length from approximately 29 to 35 amino acids, and include six conserved cysteine residues involved in disulfide bond formation and protein folding. The distribution and connection of the cysteine residues differs between the alpha and beta defensins.

EF-hand domain containing proteins-

[0017] Calcium is well known to be essential for cell signaling. However, calcium also plays a role in such cellular processes as protein processing and membrane traffic to and through the Golgi. Many proteins thought to be involved in the binding of calcium accomplish this in part through a protein calcium-binding domain known as the EF-hand domain.

[0018] The domain consists of a twelve residue loop flanked by a twelve residue alphahelical domain on both sides. In the EF hand loop, the calcium ion is situated in a coordinated pentagonal bipyramidal configuration. An invariant Glutamic acid or Aspartic acid residue provides two oxygens for liganding the calcium ion.

[0019] Proteins containing this domain include aequorin and Renilla luciferin binding protein (LBP), Recoverins, Calmodulin, Calpain small and large chains, Calretinin, Calcyclin, Fimbrin, Serine/Threonine protein phosphatase, and Diacylglycerol kinase, for example.

MAC/Perforin Family Members-

[0020] The Membrane Attack Complex (MAC) is one of the sequentially activated, membrane bound complexes of the complement system used to eliminate diseased or non-compliant cells. Under this system, activated C5b sequentially binds C6 and C7, which insert into cell membranes. This complex then binds one molecule of C8, followed by between 1 and 18 molecules of C9, which polymerizes to generate a transmembrane channel. These transmembrane channels pierce the membrane, increasing the cell's permeability. These channels permit small molecules in the cell to exchange with the medium. Therefore, water is osmotically drawn into the cell, eventually resulting in the cell bursting.

[0021] Similarly, Perforin is a molecule produced by cytotoxic T cells. In the presence of calcium, Perforin polymerizes into transmembrane channels capable of lysing a variety of target cells in a nonspecific manner.

Pancreatic Hormones-Serine Carboxypeptidases-

[0022] Pancreatic hormone (PP) is a peptide of approximately 80 amino acids in length that is generated in pancreatic islets of Langherhans and consequently secreted. Pancreatic hormone is thought to function as a regulator of pancreatic and gastrointestinal functions.

[0023] Representative members of the pancreatic hormones family of proteins include Neuropeptide Y, Peptide YY, and skin peptide YY. These proteins may be useful as therapeutics for controlling secretion of the gonadotropin-releasing hormone, disorders related to feeding, vasoconstrictory actions, and colonic mobility, as well as antibacterial and antifungal activity.

Serine Carboxypeptidases-

[0024] Carboxypeptidases catalyze the hydrolysis of C-terminal residues of polypeptides. Carboxypeptidases are identified either as metallo-carboxypeptidases or serine-carboxypeptidases.

[0025] Serine carboxypeptidases have the ability to hydrolyze peptides as well as peptide amides from the C-terminus, and have a preferential release of a C-terminal arginine or lysine residue. Their subcellular location is usually extracellular or intracellular. The catalytic activity of serine carboxypeptidases is provided by a charge relay system involving an aspartic acid residue hydrogen-bonded to a histidine, which is itself hydrogen bonded to a serine.

Tumor necrosis factors (TNF)-

Tumor necrosis factors (TNF) alpha and beta are cytokines, which act through TNF receptors to regulate numerous biological processes, including protection against infection and induction of shock and inflammatory disease. The TNF molecules belong to the "TNF-ligand" superfamily, and act together with their receptors or counterligands, the "TNF-receptor" superfamily. So far, nine members of the TNF ligand superfamily have been identified and ten members of the TNF-receptor superfamily have been characterized.

[0027] Many members of the TNF-ligand superfamily are expressed by activated T-cells, implying that they are necessary for T-cell interactions with other cell types which underlie cell ontogeny and functions (Meager, A., supra).

[0028] Considerable insight into the essential functions of several members of the TNF receptor family has been gained from the identification and creation of mutants that abolish the expression of these proteins. For example, naturally occurring mutations in the FAS antigen and its ligand cause lymphoproliferative disease (Watanabe-Fukunaga, R. et al., Nature 356:314 (1992)), perhaps reflecting a failure of programmed cell death. Mutations of the CD40 ligand cause an X-linked immunodeficiency state characterized by high levels of immunoglobulin M and low levels of immunoglobulin G in plasma, indicating faulty T-cell-dependent B-cell activation (Allen, R.C. et al., Science 259:990 (1993)). Targeted mutations of the low affinity nerve growth factor receptor cause a disorder characterized by faulty sensory innovation of peripheral structures (Lee, K.F. et al., Cell 69:737 (1992)).

[0029] TNF and LT- α are capable of binding to two TNF receptors (the 55- and 75-kd TNF receptors). A large number of biological effects elicited by TNF and LT- α , acting through their receptors, include hemorrhagic necrosis of transplanted tumors, cytotoxicity, a role in endotoxic shock, inflammation, immunoregulation, proliferation and anti-viral responses, as well as protection against the deleterious effects of ionizing radiation. TNF and LT- α are involved in the pathogenesis of a wide range of diseases, including endotoxic shock, cerebral malaria, tumors, autoimmune disease, AIDS and graft-host rejection (Beutler, B. and Von Huffel, C., *Science 264*:667-668 (1994)). Mutations in the p55 Receptor cause increased susceptibility to microbial infection.

[0030] Moreover, an about 80 amino acid domain near the C-terminus of TNFR1 (p55) and Fas was reported as the "death domain," which is responsible for transducing signals for programmed cell death (Tartaglia *et al.*, Cell 74:845 (1993)).

[0031] Plasma membrane associated proteins with a predominant tissue expression pattern are important targets for targeted drug delivery, tumor-targeted therapy (e.g., including, but not limited to, radioimmunotherapy) antibody mediated attack of diseased tissues or cancers, and immune mediated cytotoxicity.

[0032] The discovery of new plasma membrane associated proteins and the polynucleotides encoding these molecules thus satisfies a need in the art by not only providing new compositions useful in the diagnosis, treatment, and prevention of diseases associated with cell proliferation and cell signaling, particularly cancer, immune response and neuronal disorders; but also by providing new targets for immune based therapies.

Summary of the Invention

[0033] The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for

identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Detailed Description

Tables

Table 1 summarizes some of the polynucleotides encompassed by the invention [0034] (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:) and contig nucleotide sequence identifier (SEQ ID NO:X)) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to each contig sequence disclosed in Table 1. The third column provides a unique contig identifier, "Contig ID:" for each of the contig sequences disclosed in Table 1. The fourth column provides the sequence identifier, "SEQ ID NO:X", for each of the contig sequences disclosed in Table 1. The fifth column, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:X that delineate the preferred open reading frame (ORF) that encodes the amino acid sequence shown in the sequence listing and referenced in Table 1 as SEQ ID NO:Y (column 6). Column 7 lists residues comprising predicted epitopes contained in the polypeptides encoded by each of the preferred ORFs (SEQ ID NO:Y). Identification of potential immunogenic regions was performed according to the method of Jameson and Wolf (CABIOS, 4; 181-186 (1988)); specifically, the Genetics Computer Group (GCG) implementation of this algorithm, embodied in the program PEPTIDESTRUCTURE (Wisconsin Package v10.0, Genetics Computer Group (GCG), Madison, Wisc.). This method returns a measure of the probability that a given residue is found on the surface of the protein. Regions where the antigenic index score is greater than 0.9 over at least 6 amino acids are indicated in Table 1 as "Predicted Epitopes". In particular embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the predicted epitopes described in Table 1. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may

vary slightly. Column 8, "Tissue Distribution" shows the expression profile of tissue, cells, and/or cell line libraries which express the polynucleotides of the invention. The first number in column 8 (preceding the colon), represents the tissue/cell source identifier code corresponding to the key provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. For those identifier codes in which the first two letters are not "AR", the second number in column 8 (following the colon), represents the number of times a sequence corresponding to the reference polynucleotide sequence (e.g., SEQ ID NO:X) was identified in the tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of ³³P dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression. Column 9 provides the chromosomal location of polynucleotides corresponding to SEO ID NO:X. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian

Inheritance in Man, OMIMTM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/). If the putative chromosomal location of the Query overlaps with the chromosomal location of a Morbid Map entry, an OMIM identification number is disclosed in column 10 labeled "OMIM Disease Reference(s)". A key to the OMIM reference identification numbers is provided in Table 5. Column 11 provides the amino acid position of the ALOM hit(s) predicted for the amino acid sequence shown in SEQ ID NO:Y.

Table 2 summarizes homology and features of some of the polypeptides of the [0035] invention. The first column provides a unique clone identifier, "Clone ID NO:Z", corresponding to a cDNA clone disclosed in Table 1. The second column provides the unique contig identifier, "Contig ID:" corresponding to contigs in Table 1 and allowing for correlation with the information in Table 1. The third column provides the sequence identifier, "SEQ ID NO:X", for the contig polynucleotide sequence. The fourth column provides the analysis method by which the homology/identity disclosed in the Table was determined. Comparisons were made between polypeptides encoded by the polynucleotides of the invention and either a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM") as further described below. The fifth column provides a description of the PFAM/NR hit having a significant match to a polypeptide of the invention. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in columns five and six. Columns 8 and 9, "NT From" and "NT To" respectively, delineate the polynucleotides in "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth and sixth columns. In specific embodiments polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence encoded by a polynucleotide in SEQ ID NO:X as delineated in columns 8 and 9, or fragments or variants thereof.

[0036] Table 3 provides polynucleotide sequences that may be disclaimed according to certain embodiments of the invention. The first column provides a unique clone identifier, "Clone ID", for a cDNA clone related to contig sequences disclosed in Table 1. The

second column provides the sequence identifier, "SEQ ID NO:X", for contig sequences disclosed in Table 1. The third column provides the unique contig identifier, "Contig ID:", for contigs disclosed in Table 1. The fourth column provides a unique integer 'a' where 'a' is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, and the fifth column provides a unique integer 'b' where 'b' is any integer between 15 and the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. For each of the polynucleotides shown as SEQ ID NO:X, the uniquely defined integers can be substituted into the general formula of a-b, and used to describe polynucleotides which may be preferably excluded from the invention. In certain embodiments, preferably excluded from the invention are at least one, two, three, four, five, ten, or more of the polynucleotide sequence(s) having the accession number(s) disclosed in the sixth column of this Table. In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table.

Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1, column 8. Column 1 provides the tissue/cell source identifier code disclosed in Table 1, Column 8. Columns 2-5 provide a description of the tissue or cell source. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease". The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector used to generate the library.

[0038] Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 1, column 10. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of

Medicine, (Bethesda, MD) 2000. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/). Column 2 provides diseases associated with the cytologic band disclosed in Table 1, column 9, as determined using the Morbid Map database.

[0039]

Definitions

[0040] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

[0042] As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence encoding SEQ ID NO:Y or a fragment or variant thereof; a nucleic acid sequence contained in SEQ ID NO:X (as described in column 3 of Table 1) or the complement thereof; a cDNA sequence contained in Clone ID NO:Z (as described in column 2 of Table 1 and contained within the ATCC Deposit). For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a

polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown, for example, in column 2 of Table 1, each clone is identified by a cDNA Clone ID (identifier generally referred to herein as Clone ID NO:Z). Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. Furthermore, clones disclosed in this application have been deposited with the ATCC on March 24, 2000, having the ATCC designation numbers PTA-1559. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0044] In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[0045] A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), the polynucleotide sequence delineated in columns 8 and 9 of Table 2 or the complement thereof, and/or cDNA sequences contained in Clone ID NO:Z (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments, or the cDNA clone within the pool of

cDNA clones deposited with the ATCC, described herein). "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

[0046] Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

[0047] Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

[0048] Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

[0049] The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and

double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

[0050] The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA

mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

[0051] "SEQ ID NO:X" refers to a polynucleotide sequence described, for example, in Tables 1 or 2, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 6 of Table 1. SEQ ID NO:X is identified by an integer specified in column 4 of Table 1. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. "Clone ID NO:Z" refers to a cDNA clone described in column 2 of Table 1.

[0052] "A polypeptide having functional activity" refers to a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

[0053] The polypeptides of the invention can be assayed for functional activity (e.g. biological activity) using or routinely modifying assays known in the art, as well as assays described herein. Specifically, one of skill in the art may routinely assay polypeptides (including fragments and variants) of the invention for activity using assays as described in the Examples.

[0054] "A polypeptide having biological activity" refers to a polypeptide exhibiting activity similar to, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not

more than about three-fold less activity relative to the polypeptide of the present invention).

[0055] Table 1 summarizes some of the polynucleotides encompassed by the invention (including contig sequences (SEQ ID NO:X) and clones (Clone ID NO:Z) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby.

Polynucleotides and Polypeptides of the Invention

It has been discovered herein that the polynucleotides described in Table 1 are predicted to be localized to the plasma membrane of human cells. Accordingly, such polynucleotides, polypeptides encoded by such polynucleotides, and antibodies specific for such polypeptides find use in the diagnosis, treatment, and prevention of diseases associated with cell proliferation and cell signaling, particularly cancer, immune response and neuronal disorders.

Plasma membrane localization was predicted using the following method. All novel contigs in the HGS database were scored using the ALOM program developed by Klein et al. to detect potential transmembrane segments (Klein, P. et al. Biochim. Biophys. Acta 815:468 (1985); which is hereby incorporated by reference in its entirety herein). ALOM attempts to identify the most probable transmembrane segment from the average hydrophobicity value of 17-residue segments, if any. It predicts whether the segment is a transmembrane segment (INTEGRAL) or not (PERIPHERAL) comparing the discriminant score (reported as 'value') with a threshold parameter pre- defined to 0.0 for bacteria ('threshold'). For an integral membrane protein, position(s) of transmembrane segment(s) are also reported. Their length is fixed to 17 but their extension, i.e., the maximal range that satisfies the discriminant criterion, is also given in parentheses. The discrimination step mentioned above is continued after leaving out the segment till there remains no predicted transmembrane segment. The item 'count' is the number of predicted transmembrane segments.

The protein sequence used was the longest start-codon to stop-codon (or end of sequence) ORF. If the ORF was at least 100 amino acids long, and there was a predicted INTEGRAL membrane domain starting at least 40 amino acids downstream of the start

Met, the contig was selected as encoding a plasma-membrane-associated protein. The polynucleotides of the invention are predicted to be plasma membrane associated and comprise the predicted INTEGRAL membrane domains for each unique contig ID shown in column 11 of Table 1.

TABLE 1

Cone ID Contig SEQ ORF AA Predicted Epitopes Tissue Distribution Cytologic OMIM ALOM				_			_																				
Contig SEQ ORF AA Predicted Epitopes Tissue Distribution Cytologic Disease NO: X To D Thr-61 to Phe-73. AR039: 9, AR033: 5, AR089: 4, AR060: 4, AR060: 4, AR060: 4, AR060: 3, AR0	ALOM	Results			44-60							104-120,	83-99						80-104,	20-37, 56-	72, 134-	150			40-57		
Contig SEQ ORF AA Predicted Epitopes Tissue Distribution D: D (From-SEQ) Predicted Epitopes Tissue Distribution NO: X To) D (see Table IV for Library code: count Codes) 413036 11 64-471 1416 Arg-23 to Leu-33, AR033: 5, AR089: 4, AR104: 4, AR065: 3, AR065: 1, H0059: 1 and H0423: 1 456287 12 144- 1417 AR055: 15, AR060: 9, AR053: 1, AR069: 3, AR104: 1, AR039: 0 463734 13 81-530 1418 AR063: 3, AR096: 3, AR096: 2, AR069: 2, AR069: 2, AR063: 3, AR096: 2, AR069: 2, AR069: 2, AR063: 3, AR096: 3, AR096	ОМПМ	Disease	Reference(s):																								
Contig SEQ ORF AA Predicted Epitopes D: DD (From-SEQ NO: Y To)	Cytologic	Band																									
Contig SEQ ORF AA Predicted Epitopes ID: ID (From-SEQ ID)	Tissue Distribution	Library code: count	(see Table IV for Library	Codes)	AR039: 9, AR033: 5,	AR053: 5, AR089: 4,	AR096: 4, AR104: 4,	AR055: 4, AR060: 4,	AR052: 3, AR061: 3	L0619: 1, H0059: 1 and	H0423: 1.	AR055: 15, AR060: 9,	AR052: 7, AR061: 7,	AR089: 6, AR033: 6,	AR053: 5, AR096: 3,	AR104: 1, AR039: 0	L0748: 2, H0328: 1 and	H0529: 1.	4R060: 6, AR055: 3,	AR053: 3, AR096: 2,	4R089: 2, AR061: 2,	4R033: 2, AR052: 1,	4R039: 1, AR104: 1	H0031: 1		AR096: 5, AR089: 5,	4, AR052:
Contig SEQ ORF TO) NO: X TO) 413036 11 64 - 471 456287 12 144 - 572 463734 13 81 - 530 465120 14 171 - 530							7	7	7			7				7			7				7		/	7	/
Contig SEQ ORF D: DD (From- NO: X To) 413036 11 64 - 471 456287 12 144 - 572 572 463734 13 81 - 530	AA	SEQ		밁	1416							1417			-				1418						1419		
Gene Clone ID Contig SEQ No: NO: Z D: D 1 HCFNH88 413036 11 2 HODDW3 456287 12 7 7 7 12 3 HPMF138 463734 13 4 HLTDP38 465120 14	ORF	(From-	_To)		64 - 471							144 -	572						81 - 530						171 -	530	
Gene Clone ID Contig No: NO: Z ID: 1 HCFNH88 413036 2 HODDW3 456287 7 7 463734 3 HPMF138 463734 4 HLTDP38 465120	SEQ		NO: X									12							13			· 			14		
Gene Clone ID No: NO: Z 1 HCFNH88 2 HODDW3 3 HPMFI38 4 HLTDP38	Contig	Ä															_	•	463734								
Gene No: 3	Clone ID	NO: Z			HCFNH88							норрмз	7						HPMFI38						HLTDP38		
	Gene	No:			-														3						4		

							90-113,	59-78, 2-	18, 28-44						31-57, 63-	85, 4-23								126-143	,			
		_	_		· -																			126650,	126650,	164860,	180105,	222800,
	-												<u></u>											7q31				
AR061: 4, AR053: 3,	AR039: 2, AR104: 1	L0662: 3, L0803: 2,	L0805: 2, T0002: 1, H0090:	1, H0412: 1, L0794: 1,	L0804: 1, L0655: 1, L0647:	1, L0666: 1 and L0663: 1.	AR055: 6, AR060: 4,	AR052: 4, AR061: 3,	AR039: 3, AR089: 3,	AR053: 3, AR096: 3,	AR033: 3, AR104: 2	L0615: 1, S0420: 1,	H0333: 1, H0286: 1, H0634:	1, H0144: 1 and H0423: 1.	AR033: 8, AR055: 5,	AR053: 3, AR089: 3,	AR052: 3, AR061: 3,	AR039: 3, AR060: 3,	AR104: 2, AR096: 2	L0756: 4, L0439: 2,	S0412: 2, S0222: 1, H0327:	1, H0009: 1, L0157: 1 and	S0031: 1.	AR089: 7, AR096: 6,	AR053: 5, AR060: 5,			AR033: 3, AR061: 1
							Gln-20 to Ala-26,	Ser-53 to Glu-60.																Met-1 to Phe-6,	Ser-12 to Asp-17,	Ser-100 to Ser-105,	Arg-163 to Asp-176, AR104:	Val-192 to Glu-199.
							1420								1421									1422				
							15 - 365								164 -	595								67 - 723				
							15								16									17				
							465711								466000									488966				
							HMHBT30				_	_			HFCBA57									HSRAL33		_		
							S								9									7				

	89-105	72-90
246900, 274600, 274600, 602081		
L0758: H0328: L, L0803: L, H0627:	5, 3, 3 1, 1,	117, 111, 72, 66, 21 20731: 1,
L0777: 4, L0766: 3, H0014: 2, L0731: 2, L0758: 2, S0282: 1, S0007: 1, S0280: 1, H0575: 1, H0328: 1, L0369: 1, L0637: 1, L0771: 1, L0768: 1, L0803: 1, L0655: 1, L0809: 1, S0380: 1, H0521: 1, H0627: 1, S3014: 1, L0748: 1, L0608: 1, S0011: 1 and S0192: 1.	AR055: 8, AR052: 5, AR033: 4, AR061: 4, AR060: 4, AR089: 3, AR096: 3, AR039: 3, AR104: 3, AR053: 3 L0596: 2, L0588: 2, H0135: 1, H0056: 1, L0369: 1, L0803: 1, H0520: 1, S0027: 1 and S0276: 1.	AR060: 140, AR055: 117, AR104: 113, AR039: 111, AR061: 92, AR033: 72, AR053: 70, AR052: 66, AR089: 55, AR096: 21 L0748: 5, L0749: 5, L0439: 3, L0779: 2, L0731: 2, H0556: 1, S0356: 1, H0575: 1, H0597: 1, H0551
S 1, S 1, S 1, E 1, E	Pro-52 to Pro-57. AJ A	Leu-9 to Arg-18, AF Phe-109 to Gly-115. AF AF AF AF AF AF LO LO LO
	1423	1424
	7 18 20 - 415	19 74 - 424
•	HSSMQ84 502907	HUKAB82 503441
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	22-68	100-118
1, H0413: 1, H0059: 1, L0770: 1, L0771: 1, L0655: 1, H0144: 1, S0378: 1, L0747: 1 and S0276: 1.	AR096: 4, AR033: 3, AR039: 3, AR089: 3, AR055: 3, AR052: 2, AR061: 2, AR053: 1, AR060: 1, AR104: 1 L0766: 4, H0617: 2, L0662: 2, H0690: 2, H0295: 1, H0662: 1, S0354: 1, H0729: 1, H0318: 1, H0545: 1, H0266: 1, H0401: 1, H0135: 1, H0087: 1, L5575: 1, L0803: 1, L0523: 1, L0383: 1, L0665: 1, H0703: 1, H0539: 1, H0521: 1, H0522: 1, S0406: 1, S0028: 1, L0779: 1 and H0352: 1.	AR052: 5, AR053: 5, AR096: 4, AR055: 4, AR089: 4, AR033: 3, AR060: 3, AR039: 2, AR104: 2, AR061: 2 L0775: 3, H0624: 2, L0471: 2, S0051: 2, L0768: 2, H0659: 2, L0759: 2, L0605: 2, S0192: 2, S0114:
		Met-1 to Arg-11, Gly-30 to Arg-39.
	1425	1426
	29 - 328	72 - 425
	20	21
	506828	506893
	HDPPP46	HMTME11
	10	11

	9-41, 83- 106, 54-76
1, S0116: 1, H0638: 1, H0125: 1, H0489: 1, S0222: 1, L0623: 1, T0115: 1, H0327: 1, H0687: 1, T0023: 1, H0031: 1, H0673: 1, L0065: 1, L0520: 1, L0769: 1, L0653: 1, L0783: 1, L0809: 1, L0519: 1, L0543: 1, H0672: 1, S0330: 1, S0378: 1, S0380: 1, H0525: 1, H0436: 1, S3012: 1, L0777: 1, L0731: 1, H0653: 1, H0543: 1, H0422: 1 and H0543: 1,	AR055: 11, AR060: 8, AR033: 5, AR061: 5, AR052: 5, AR089: 4, AR104: 4, AR096: 4, AR039: 4, AR053: 4 L0439: 4, L0803: 3, H0590: 2, L0483: 2, H0163: 2, L0805: 2, S0374: 2, H0658: 2, H0696: 2, H0717: 1, S0116: 1, S0358: 1, L0717: 1, H0052: 1, H0194: 1, H0184: 1, L0738: 1, H0545: 1, S0316: 1, S0003: 1, S0364: 1, S0366: 1, S0036: 1, H0272: 1, L0638:
	1427
	12 - 386
	53
	507310
	HBMUK46
	12

	138-154, 8-24	62-89, 25- 46
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4: 5:	8: 5: 72: 58:	33:
1, L0766: 1, L0776: 1, L0789: 1, L0664: 1, L0665: 1, H0710: 1, H0521: 1, S0013: 1, S0406: 1, L0744: 1, L0752: 1, L0758: 1, L0605: 1, S0026: 1 and H0543: 1.	AR052: 319, AR096: 250, AR089: 171, AR060: 143, AR053: 121, AR104: 71, AR053: 57, AR033: 51, AR061: 51, AR055: 14 L0752: 3, L0748: 2, L0740: 2, L0731: 2, S0358: 1, H0438: 1, H0574: 1, H0046: 1, H0041: 1, H0272: 1, S0150: 1, L0794: 1, L0803: 1, L0804: 1, L0775: 1, L0661: 1, L0789: 1, H0672: 1, H0539: 1, L0758: 1 and S0436: 1.	AR033: 1, AR089: 1, AR053: 1, AR104: 1, AR061: 1, AR096: 0, AR055: 0, AR060: 0, AR052: 0 L0766: 6, L0740: 5, H0135: 1, L0769: 1, L0383: 1, S0044: 1, L0750: 1 and
		1429 Pro-15 to Ser-21, Ser-60 to Tyr-65, Glu-90 to Asp-101.
	1428	1429
	25 - 597	60 - 362
	23	24
	509728	521848
	HETDT70	HPWBL19
	13	14

							,																				
	88-104, 49-65							96-113																			
			<u>-</u>	_	_						-													-			
	2, AR053: 2, 1, AR104: 1,	1, AR055: 1,	1, AR096: 0,	0, AR052: 0	S0007: 2, H0392: 2,	L0745: 1, L0753: 1, L0759:	89: 1.	1, AR096: 1,	1, AR089: 1,	1, AR061: 1,	0, AR055: 0,	0, AR039: 0	L0766: 5, L0438: 4,	L0439: 4, L0803: 3, L0759:	3, H0445: 3, H0046: 2,	L0157: 2, L0762: 2, L0363:	2, L0774: 2,	L0776: 2, L0790: 2, L0666:	2, H0144: 2, L0748: 2,	_0749: 2, H0556: 1, H0159:	1, H0716: 1, H0459: 1,	S0418: 1, L0005: 1, H0580:	1, S0046: 1, H0612: 1,	H0586: 1, H0050: 1, L0471:	1, H0615: 1, H0488: 1,	S0426: 1, H0529: 1, L0520:	1, L0638: 1, L0667: 1,
L0752: 1.	AR033: AR089:	AR061:	AR060:	AR039:	S0007: 2	L0745: 1,	1 and L0589: 1.	AR104:	AR033:	AR060:	AR052:	AR053: (3, H0445:	L0157: 2,	2, L0794:	L0776: 2,	2, H0144:	L0749: 2,	1, H0716:	S0418: 1,	1, S0046:	H0586: 1,	1, H0615:	S0426: 1,	1, L0638:
								Lys-12 to Lys-17,	Thr-39 to Lys-45,	Thr-49 to Glu-57,	Thr-59 to Glu-69,	Glu-80 to Ile-90,	Gly-122 to Met-127,	Lys-170 to Asn-177.													-
	1430							1431							·												
	48 - 422			,				68 - 598									_					-		,			
į	25							26					_														
	523186							524559																	-		
	HMKAD85							HE9NE12		. = 1,0				-								•					
	15							16																			

	81-102, 22-38	64-80, 15-
	148370	
,	8p23	
L0373: 1, L0378: 1, L0805: 1, L0659: 1, L0526: 1, L0809: 1, L0663: 1, S0374: 1, H0711: 1, H0670: 1, H0521: 1, L0777: 1, L0780: 1, L0485: 1, L0097: 1, S0192: 1, H0543: 1, H0423: 1 and H0506: 1.	561: 4, 555: 3, 560: 3, 96: 2, 104: 1	AR055: 16, AR061: 7, AR052: 7, AR060: 6, AR033: 5, AR089: 5, AR039: 0, AR104: 0 H0052: 5, L0748: 5, L0756: 4, L0731: 4, S0360: 3, L0764: 3, L0747: 3, L0749: 3, H0255: 2, H0333: 2, L0055: 2, L0653: 2, L0740: 2, L0754: 2, L0750: 2, L0596: 2, H0352: 2, H0556: 1, H0341: 1, H0662: 1, H0306: 1, H0402: 1, H0036: 1, H0434: 1, H0150:
	Leu-15 to Ser-21.	Arg-56 to Phe-61.
	1432	1433
	12 - 317	53 - 376
	27	28
	525950	527491
	HE2AX73	HHGBV89
	17	18

	48-65	125-157, 4-29, 67- 86, 36-52, 106-122
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.0521: .0684: .0755:	14, 11, 10, 9, 8 10333: 1, 2,0666:	1, 1, 1, 0, 0, 0282:
1, H0252: 1, L0456: 1, H0135: 1, H0413: 1, H0059: 1, H0529: 1, L0770: 1, L0769: 1, L0630: 1, L0521: 1, L0662: 1, L0775: 1, L0776: 1, L0493: 1, H0684: 1, S0328: 1, S0044: 1, L0777: 1, L0752: 1, L0755: 1, L0758: 1 and S0242: 1.	AR039: 14, AR055: 14, AR033: 11, AR053: 11, AR052: 11, AR060: 10, AR104: 10, AR096: 9, AR089: 8, AR061: 8 S0380: 2, L0742: 2, L0779: 2, L0759: 2, H0333: 1, H0039: 1, H0040: 1, H0625: 1, H0561: 1, L0666: 1, L0663: 1, H0672: 1, L0747: 1, L0777: 1, L0758:	AR089: 1, AR061: 1, AR053: 1, AR096: 1, AR060: 1, AR104: 1, AR033: 0, AR055: 0, AR039: 0, AR052: 0 L0777: 5, S0436: 5, S0116: 3, L0805: 3, L0809: 3, H0696: 3, H0423: 3, S0282:
1, H0252: 1 H0135: 1, 1 1, H0529: 1, L L0769: 1, I 1, L0662: 1 L0776: 1, I 1, S0328: 1 L0777: 1, I	AR039: 14, AR055: AR033: 11, AR053: AR052: 11, AR060: AR104: 10, AR096: AR089: 8, AR061: S0380: 2, L0742: 2, L0779: 2, L0759: 2, H 1, H0039: 1, H0040: 1 H0625: 1, H0561: 1, I 1, L0663: 1, H0672: 1 L0747: 1, L0777: 1, L 1 and H0444: 1.	AR089: 1, AR061: 1 AR053: 1, AR104: 1 AR033: 0, AR055: 0 AR039: 0, AR052: 0 L0777: 5, S0436: 5, S 3, L0805: 3, L0809: 3, H0696: 3, H0423: 3, S
	Asp-24, Arg-40.	Asn-54 to Gly-60, Pro-166 to Pro-171.
	Lys-13 to Asp-24, Pro-32 to Arg-40.	Asn-54 to Gly-60, Pro-166 to Pro-17
	1434	1435
	1 - 405	531 - 16
	53	30
	529791	532045
	HTTDC06	HFXKR35
	19	20

	56-73
767: 557: 740: 774: 708: 774: 766: 755:	
2, \$0354: 2, H0083: 2, H0316: 2, L0766: 2, L0776: 2, \$0406: 2, L0779: 2, \$0414: 1, H0657: 1, H0656: 1, \$0358: 1, \$0444: 1, \$0360: 1, H0340: 1, H0559: 1, H0619: 1, H0559: 1, H0619: 1, H0615: 1, H0618: 1, H0619: 1, H0615: 1, H0618: 1, H0619: 1, H0659: 1, H0659: 1, L0653: 1, L0669: 1, L0664: 1, H0659: 1, L0761: 1, L0668: 1, L0760: 1, L07	AR055: 4, AR039: 3, AR060: 2, AR033: 2, AR053: 2, AR061: 2,
<u> </u>	Ser-7 to Gln-20, Pro-24 to Phe-34, A Gly-76 to Gly-84.
	1436
	17 - 373
	31
	534414
	HHSDL85
	21

			
	49-65	49-65	46-62, 26- 42
			114240, 224120, 600839, 602099
			15q15.1
AR104: 2, AR089: 2, AR096: 2, AR052: 2 S0007: 3, S0001: 1, H0618: 1, H0009: 1, S0051: 1, L0763: 1, L0439: 1 and L0758: 1.	AR033: 54, AR055: 51, AR061: 43, AR089: 40, AR053: 38, AR060: 38, AR052: 26, AR096: 11, AR104: 10, AR039: 5 H0038: 2	AR033: 112, AR052: 80, AR096: 68, AR053: 67, AR089: 65, AR104: 61, AR060: 58, AR061: 55, AR039: 52, AR055: 38 H0052: 2, H0616: 2, L0779: 2, L0777: 2, H0656: 1, H0549: 1, H0038: 1, L0748: 1, L0758: 1, L0601: 1 and H0543: 1.	AR055: 17, AR053: 9, AR060: 9, AR033: 9, AR061: 8, AR039: 7, AR089: 6, AR052: 6, AR104: 6, AR096: 5 S0418: 3, L0439: 3, L0595: 2, H0542: 2, H0656:
	Pro-15 to Thr-24, Glu-39 to Trp-47.	Arg-14 to Asp-20.	
	1437	1438	1439
	88 - 438	37 - 453	156 - 488
	32	33	34
	535036	535040	536712
	HTECA32	нтенг.79	HPJBL54
	22	23	24

	81-98, 13- 29, 175- 191, 62-78	177-193,
& .2	· .::	4. K
1, H0638: 1, S0420: 1, S0045: 1, H0253: 1, H0267: 1, H0553: 1, S0150: 1, L0438: 1, H0519: 1, S0126: 1, H0660: 1, S0152: 1 and H0543: 1.	AR096: 1, AR055: 1, AR089: 1, AR060: 1, AR039: 1, AR033: 0, AR061: 0, AR053: 0, AR052: 0, AR104: 0 S0028: 3, S0001: 2, H0617: 2, L0361: 2, S0356: 1, S0045: 1, H0619: 1, S0278: 1, H0250: 1, H0231: 1, H0181: 1, S0390: 1 and S0031: 1.	AR052: 3, AR096: 2, AR053: 2, AR033: 2, AR089: 2, AR061: 2, AR104: 1, AR055: 1, AR104: 1, AR039: 0 L0789: 4, H0306: 2, L0809: 2, L0759: 2, L0596: 2, H0402: 1, H0580: 1, H0550: 1, H0486: 1, H0559: 1, H0486: 1, H0031: 1, H0674: 1, H0135: 1, H0100: 1, L0800: 1,
	Asp-46 to Glu-59.	
	1440	1441
	64 - 753	588-929
	35	36
	538217	550208
	HSDDD20	HCUCG74
	25	26

VO 01/90304		FC1/0501/10-
	38-59	7-37, 89-
L0794: 1, L0804: 1, L0805: 1, L0515: 1, L0783: 1, H0672: 1, L0777: 1, H0444: 1 and H0352: 1.	AR033: 4, AR089: 3, AR060: 2, AR055: 2, AR052: 1, AR053: 1, AR061: 1, AR096: 0, AR039: 0, AR104: 0 S0242: 1 and S0196: 1.	AR089: 45, AR096: 43, AR060: 39, AR039: 37, AR055: 27, AR104: 20, AR033: 20, AR052: 19, AR053: 14, AR061: 14 H0250: 60, S0126: 24, H0013: 9, H0124: 9, H0494: 8, H0521: 7, H0428: 6, H0553: 6, H0644: 6, H0038: 6, S0027: 6, S0040: 5, T0039: 5, H0551: 5, T0067: 5, H0171: 4, S0356: 5, S0028: 5, L0439: 5, L0740: 5, H0171: 4, S0356: 4, S0046: 4, H0589: 4, H0046: 4, H0024: 4, H0266: 4, S0003: 4, H0040: 4, H0059:
,		Pro-69 to Gln-77.
	1442	1443
	96 - 404	24 - 362
	37	∞ ∞
	550992	551777
	HFIXK94	HPJAV46
	27	28

4, S0152: 4, L0603: 4, H0556: 3, S0222: 3, H0574:	3, H0156: 3, S0010: 3,	HUS81: 3, HU620: 3, H0014: 3, H0015: 3, H0373: 3.	S0022: 3, H0031: 3, H0547:	3, H0519: 3, H0522: 3,	L0748: 3, H0624: 2, H0265:	2, H0295: 2, S0212: 2,	H0484: 2, H0661: 2, H0125:	2, S0418: 2, H0208: 2,	S0045: 2, H0619: 2, H0645:	2, H0550: 2, H0431: 2,	H0370: 2, H0427: 2, H0575:	2, H0618: 2, S0049: 2,	H0530: 2, H0545: 2, H0012:	2, H0375: 2, H0179: 2,	H0286: 2, H0615: 2, H0039:	2, H0622: 2, H0032: 2,	H0068: 2, H0090: 2, H0616:	2, H0264: 2, H0268: 2,	H0100: 2, T0042: 2, S0294:	2, S0142: 2, H0517: 2,	H0651: 2, S0037: 2, H0506:	2, H0157: 1, H0294: 1,	H0671: 1, H0662: 1, S0420:	1, S0358: 1, S0376: 1,	S0360: 1, H0580: 1, H0393:	1, H0437: 1, H0369: 1,	H0549: 1, H0357: 1, H0409:
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	<u> </u>																<u>.</u>											
:04		121:		386:)23:		34:		<u>4</u>		36:		523:		6		<u>‡</u>	-	84:		558:		136:		46:	 -	81:
$^{:1,}_{,\mathrm{T0C}}$; T,	, H0	;; ;;	, HOC	: 1 ,	, H0	: 1,	, S03	1,	S02	: 1,	, SOC	1,	, H0	: 1,	, S04	: 1,	S03	۲,	, L03	1,	, H0	: 1,	, H04	1,	107	Η,	L05
1, H0602: 1, H0587: 1, H0642: 1, L0477: 1, T0	1, H0635: 1, H0097: 1,	46: 1	1, H0230: 1, H0196: 1,	15: 1	l, H0009: 1, H0081: 1,	H0197: 1, H0023: 1, H0023:	1, H0107: 1, T0010: 1,	18: 1	1, S0316: 1, H0284: 1,	50: 1,	l, H0328: 1, L0483:	08: 1	1, H0634: 1, H0488: 1,	H0433: 1, H0056: 1, H0623:	l, T0069: 1, H0560: 1,	H0561: 1, S0448: 1, S0440:	1, H0509: 1, H0131: 1,	S0150: 1, S0144: 1, S0344:	1, S0208: 1, S0210: 1,	29: 1)148:	H0593: 1, H0435: 1, H0658:	1, H0666: 1, H0518: 1	S0004: 1, H0134: 1, H0436:	1, S0432: 1, S0390: 1	S3014: 1, L0754: 1, L0746:	0596	L0605: 1, L0592: 1, L0581:
: 1, F , L04	: 1, E	, S03	: 1, H	, T01	: 1, H	, HOC	: 1, T	, S03	1, H	S02;	: 1, L	, H07	1, H	, H0C	1, H	, S04	: 1, H	S01 ²	1, S(H05	1, S(, H04	: 1, H	H01	1, S(L07	1, L	L05
0602 42: 1	0635	36: 1	0230	51: 1	6000	97:1	0107	71:1	3316:	[4: 1,	0328	12: 1	0634	33: 1	:6900	61:1	0509	50: 1,)208:	26: 1,)216:	93: 1	9990	4: 1,	432:	4: 1,	7758:	5:1,
1, H H06	1, H	00 <u>H</u>	1, H	H02	1, H	H01	1, H	H02	1, S(S03	1, H	H02	1, H	H04	1, T	H05	1, H	<u>S01</u>	1, S(S04,	1, S(H05	1, H	<u> </u>	1, S(S30.	<u>1, L</u>	106
	•																								-			
		<u> </u>			_																							
			_					-							-													
											•																	
																						-						
			_																	_								

	42-67, 3-	36-61, 92- 110	1-33, 230- 247, 125- 141
1, L0593: 1, L0595: 1, S0011: 1, H0668: 1, S0026: 1, S0446: 1 and H0293: 1.	AR053: 16, AR096: 14, AR052: 14, AR055: 13, AR089: 11, AR060: 9, AR033: 9, AR104: 6, AR061: 5, AR039: 3 H0038: 8, H0616: 4, L0779: 3, L0758: 3, L0753: 2, L0032: 1, T0006: 1, H0040: 1, S0002: 1, L0768: 1, S0053: 1 and H0547: 1.	AR039: 13, AR053: 11, AR055: 9, AR089: 9, AR033: 9, AR060: 7, AR096: 7, AR052: 7, AR061: 5, AR104: 5 S0222: 1	AR052: 4, AR061: 3, AR055: 3, AR053: 3, AR089: 2, AR033: 2, AR060: 2, AR039: 1, AR096: 1, AR104: 1 S0002: 70, S0426: 29, S0278: 28, S0003: 28, H0521: 28, S0344: 27, S0142: 14, L0747: 14, H0090: 13, S0144: 13,
		Ser-60 to Ser-66.	Arg-35 to Cys-46, Phe-52 to Met-57, Thr-70 to Gly-84, Thr-88 to Glu-109, Gly-151 to Gly-159, Ser-167 to Thr-175, Ala-193 to Phe-206, Arg-215 to Gly-223.
	1444	- 1445	1446
	21 - 329	885	401 - 1144
	39	9	41
	558312	561612	562024
	HTTDL61	HFPBN94	HYBBG69
	53	30	31

																											-		
S0126: 13, H0580: 10,	S0214: 10, H0591: 10,	L0659: 10, L0731: 10,	H0575: 9, S0360: 8, H0046:	8, L0759: 8, H0586: 6,	H0545: 6, L0771: 6, L0663:	6, L0756: 6, H0013: 5,	H0042: 4, H0622: 4, H0040:	4, H0522: 4, L0777: 4,	H0587: 3, H0318: 3, H0581:	3, H0546: 3, H0014: 3,	L0163: 3, H0030: 3, L0775:	3, L0651: 3, L0805: 3,	L0606: 3, S0374: 3, H0519:	3, H0518: 3, L0740: 3,	L0755: 3, H0583: 2, S0116:	2, H0637: 2, H0486: 2,	H0251: 2, H0012: 2, H0375:	2, H0416: 2, S0250: 2,	H0553: 2, H0163: 2, H0038:	2, H0063: 2, H0538: 2,	L0770: 2, L0646: 2, L0662:	2, L0649: 2, L0666: 2,	L0565: 2, S0328: 2, S0380:	2, S0044: 2, L0744: 2,	L0750: 2, L0752: 2, L0758:	2, S0031: 2, L0591: 2,	L0599: 2, H0668: 2, S0192:	2, S0194: 2, S0282: 1,	H0661: 1, H0662: 1, H0306:
-																													
																					-								

		35-62
1, 1, 1, 1, 1, H0036: 1, H0039: 1, H0100: 1, L0763: 1, L0561: 1, L0653: 1, L0782: 1, H0684:	312: 597:	
1, H0638: 1, S0358: 1, S0376: 1, T0008: 1, S0132: 1, H0619: 1, H0645: 1, H0351: 1, H0427: 1, S0280: 1, L0022: 1, T0082: 1, H0030: 1, H0039: 1, H0030: 1, H0030: 1, H0031: 1, H0039: 1, H0031: 1, H0674: 1, H0674: 1, H0674: 1, H0674: 1, H0674: 1, L0143: 1, H0673: 1, H0674: 1, L0143: 1, H0673: 1, H0674: 1, L0143: 1, L0763: 1, L0769: 1, L0764: 1, L0769: 1, L0764: 1, L0803: 1, L0774: 1, L0803: 1, L0776: 1, L0657: 1, L0769: 1, L0657: 1, L0769: 1, L0657: 1, L0769: 1, L0657: 1, L0776: 1, L0657: 1, L0776: 1, L0657: 1, L0779: 1, L0657: 1, L0779: 1, L0657: 1, L0779: 1, L0657: 1, L0779: 1, L0657: 1, H0684: 1, H0643: 1, H0643: 1, H0642: 1, H0643: 1, H0642: 1, H0643: 1, H0642: 1, H0643: 1, H0642: 1, H06	S0330: 1, H0555: 1, S3012: 1, L0748: 1, L0757: 1, H0595: 1, L0584: 1, L0597: 1 and H0352: 1.	AR096: 1, AR089: 1,
1, 1 1, 1	S03 1, L H05	
		17 Met-1 to Gly-6,
		350 - 144
	<u></u>	42 3.
		562077
		HDPOJ05
		32

	42-66, 67- 84, 9-25
\cdots	AR052: 7, AR053: 4, AR089: 3, AR060: 3, AR096: 3, AR033: 2, AR061: 2, AR039: 2, AR055: 2, AR104: 2 S0278: 1 and H0445: 1.
	Leu-30 to Thr-35, Phe-38 to Gly-44.
	39 - 428 1448
	562775 43
	33 HMAGF64

			.,
138-155, 83-99, 35- 51, 59-75	23-40, 50- 66	71-87, 98-	73-89,
AR053: 12, AR052: 11, AR089: 8, AR096: 8, AR055: 7, AR060: 7, AR033: 5, AR061: 5, AR104: 4, AR039: 3 T0023: 2, L0662: 2, S0330: 2, L0749: 2, L0758: 2, S0356: 1, S0358: 1, S0360: 1, S0408: 1, L0586: 1, S0280: 1, H0590: 1, H0581: 1, H0052: 1, H0014: 1, S0003: 1, H0316: 1, H0591: 1, S0450: 1, S0150: 1, S0426: 1, L0766: 1, S0216: 1, L0747: 1, L0756: 1, L0752: 1 and L0596: 1.	AR039: 35, AR053: 29, AR104: 28, AR033: 25, AR052: 23, AR096: 22, AR055: 19, AR089: 18, AR060: 13, AR061: 10 H0555: 1	AR096: 2, AR089: 1, AR039: 1, AR052: 1, AR033: 1, AR104: 1, AR060: 0, AR061: 0, AR055: 0 H0600: 1 and S0002: 1.	AR096: 14, AR089: 12,
1449 Lys-14 to Asp-24, AR053: Gln-114 to Leu-119, AR089: Asp-122 to Arg-127. AR055: AR104: T0023: S0330: 2, S0356: S0360: 1, S0286: 1, S0003 H0591: 1, S0426: 1, L0752	1450 Met-1 to Gly-6.	•	
1449	1450	1451	1452
143 - 700	14 - 355	296 - 670	93 - 473
4	45	46	47
563589	567314	571474	572607
34 HACCO38 563589	HRAAM31	HWDAA0 3	нтнсу60
	35	36	37

111-127, 34-50	84-101	88-89	81-115
AR055: 8, AR060: 8, AR052: 8, AR033: 6, AR053: 6, AR039: 4, AR061: 4, AR104: 3 H0556: 1, H0050: 1, H0063: 1 and H0494: 1.	AR039: 14, AR033: 10, AR053: 9, AR055: 7, AR104: 7, AR089: 7, AR096: 6, AR052: 5, AR060: 5, AR061: 4 L0741: 3, L0438: 2, S0222: 1, H0427: 1, H0618: 1, H0253: 1, H0284: 1, S0038: 1, H0494: 1, S0144: 1, L0743: 1 and L0366: 1.	AR089: 4, AR096: 3, AR033: 3, AR052: 3, AR060: 2, AR055: 2, AR053: 1, AR061: 1, AR104: 1, AR039: 0 H0422: 2, H0339: 1 and 0769: 1.	AR055: 11, AR060: 7, AR052: 5, AR089: 5, AR061: 5, AR033: 5, AR053: 5, AR096: 4, AR039: 4, AR104: 3 L0747: 3, L0754: 2,
AR055: AR052: AR053: AR061: H0556: H0063: 1	AR039: AR053: AR104: AR096: AR060: L0741: S0222: 1 1, H0253 S0038: 1 1, L0743	AR089: AR033: AR060: AR053: AR104: H0422: L0769: 1	AR055: AR052: AR061: AR053: AR039: L0747:
		Lys-22 to Gly-28, Lys-39 to Glu-48, Ser-54 to Trp-59.	1455 His-13 to Ser-21.
	1453	1454	1455
	15 - 428	70 - 438	356 - 700
	84	49	50
	573110	573179	573751
	HTLEV17	HCFAB91	HMWEE18
	38	39	4

-	46-62	61-79
	-	
L0599: 2, H0713: 1, H0341: 1, S0360: 1, H0601: 1, H0592: 1, H0123: 1, H0494: 1, H0660: 1, L0756: 1 and L0779: 1.	AR053: 16, AR052: 14, AR096: 12, AR089: 10, AR104: 7, AR080: 6, AR104: 7, AR060: 6, AR055: 6, AR033: 5, AR061: 3, AR039: 3 H0617: 7, L0438: 6, L0439: 5, H0253: 4, L0794: 3, L0766: 3, L0791: 3, H0618: 2, S0344: 2, L0769: 2, L0662: 2, L0758: 2, H0556: 1, H0733: 1, H0333: 1, T0040: 1, H0013: 1, H0575: 1, H0013: 1, H0575: 1, H0023: 1, H0606: 1, L073: 1, H0606: 1, H0135: 1, T0004: 1, H0509: 1, S0144: 1, L0803: 1, L4501: 1, L0663: 1, L0565: 1, H0672: 1, H0631: 1, L0744: 1, L0747: 1, L0756: 1, L0779: 1, L0731: 1, S0436: 1, S0194: 1 and H0542: 1	AR055: 14, AR060: 13,
<u> </u>		Leu-3 to Gln-18. A
	1456	1457
	46 - 354	225 -
	51	52
	574924	575287
	HTLA185	ннРСО38
	14	42

	68-86, 89- 108, 40-56	63-84	53-75, 92- 112, 25-45
: 10, 8, 5, 0 1,	3, 1, 1, 0, 0, and	2, 1, 1, 18: 1.	4, 2, 2, 2, H0657:
AR089: 12, AR096: 10, AR052: 8, AR033: 8, AR061: 7, AR053: 5, AR104: 0, AR039: 0 L0756: 2, H0051: 1, S0380: 1, L0748: 1 and L0753: 1.		1	5, AR052: 4, AR053: 3, AR060: 2, AR061: 1 4, L0803: 3 2, L0526: 2,
AR089: AR052: AR104: L0756: S0380: 1 L0753: 1		AR060: AR033: AR061: AR096: AR039: H0123:	AR033; AR089: AR055; AR096: AR039: L0438: H0169: 2
	Gln-22 to Gly-28, Thr-109 to Gly-114, Phe-117 to Arg-124.	1459 Gly-35 to Gln-41, Phe-51 to Lys-57.	
	1458	1459	1460
530	229 - 639	252 - 551	73 - 426
	53	54	55
	576739	578925	581501
	HNGER82	HBJLU13	HCFDC55
	43	4	45

	83-101, 62-78	66-82	57-86
			102200, 106100,
			11q13
H0050: 1, S0370: 1, L0637: 1, L0646: 1, L0800: 1, L0662: 1, L0766: 1, L0607: 1, L0659: 1, L0659: 1, H0659: 1, H0659: 1, S0328: 1, H0436: 1, L0777: 1, L0752: 1, S0242: 1 and H0422: 1.	AR053: 2, AR089: 2, AR060: 2, AR096: 1, AR055: 1, AR061: 1, AR033: 1, AR104: 1, AR039: 0, AR052: 0 H0012: 3, L0794: 3, L0766: 2, L0788: 2, S0192: 2, H0618: 1, H0015: 1, H0073: 1, T0023: 1, H0063: 1, L0763: 1, L0787: 1, L0532: 1, S3012: 1, S0027: 1, L0747: 1, L0750: 1, L0731: 1 and S0276: 1.	AR055: 15, AR039: 15, AR033: 13, AR104: 12, AR061: 12, AR053: 10, AR089: 9, AR060: 9, AR052: 8, AR096: 8 L0748: 2 and H0575: 1.	AR033: 4, AR089: 3, AR096: 2, AR061: 2,
	Leu-12 to Gly-18, Tyr-27 to Glu-34, Lys-127 to Pro-132.	Lys-2 to Ser-10, Gln-20 to Leu-25, Val-29 to Arg-53.	1463 Gly-2 to Leu-7, Pro-11 to Leu-26,
	1461	1462	1463
	178 - 591	13 - 330	660 - 331
	56	57	58
	586810	587520	589293
	HFKCT25	HAPOW05	HCUFP05
	46	47	48

W U 01/90304	FC1/USU1/1043(
	56-72, 1- 17, 76-92
131100, 131100, 131100, 133780, 147050, 164009, 168461, 168461, 188461, 180721, 180840, 191181, 193235, 209901, 259700, 259700, 600045, 600528, 601884	Xq22.3-q23 300046, 300067, 300067, 300121,
AR060: 2, AR055: 2, AR104: 1, AR039: 0, AR052: 0, AR053: 0 L0769: 9, L0752: 6, L0747: 5, L0759: 5, L0764: 4, L0806: 4, L0759: 5, L0764: 4, L0806: 4, L0770: 3, L0783: 3, L0750: 3, S0408: 2, H0549: 3, L0770: 3, L0783: 3, L0750: 3, S0408: 2, L0794: 2, L0771: 2, L0662: 2, L0776: 2, L0809: 2, L0779: 2, L0776: 2, L0756: 2, L0779: 2, L0757: 2, H0402: 1, H0664: 1, H0402: 1, H0014: 1, H0688: 1, L0709: 1, L0709: 1, L0763: 1, L0763: 1, L0765: 1, L0768: 1, L0763: 1, L0767: 1, L0800: 1, L0773: 1, L0800: 1, L0773: 1, L0800: 1, L0773: 1, L0800: 1, L0774: 1, L0803: 1, L0777: 1 and L0786: 1, L0777: 1 and	4 –
Gly-28 to Ala-40, Arg-51 to Pro-58, Asp-92 to Leu-97.	Gln-28 to Pro-41, Lys-94 to Pro-108.
	1464
	161 -
	59
	597069
	HE8CX53
	49

	4									Į,	16-								
	42-60, 4-										47-66, 16-								
	42	22									47	32							
300121, 301201, 301835, 311850	162400,	227645,	229700,	278700,	601309,	601309,	602014,	602088			129010,	154545,	.761,	164761,	164761,	164761,	188550,	601386,	601493
300 301 311 311	162	227	229	278	90	601	902	905		-	129	154	<u>1</u>	<u>16</u>	<u>2</u>	16	188	601	60
											4								
	9q22.1-	q <u>2</u> 2.3									10q11.2-	11.1							
	8	8		_			7:	_		+	<u> </u>	6							
5 L075 2, H015 H010 H010 1,	15,	۸,	ĸή	4,	33		L015		H014		_	T,	ó	ó	0	6:8			
339: 38: 4, 33: 3, 3, 329: 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3,	033:)61:	96:	55:	960:	1:2,	F. 1,]	. [69	i: 1, 1		55:	:680	900:	333:	39:	S018			
ARC 10001; 1, HOO 00001 1, HOO 00038 00038 1054 8: 1.	, AR	5, AR061:	AR(AR(4, AR060:	S000	[019	,150	0794	 - 	AR(AR(AR(0, AR033:	0, AR039:	and			
: 6, 9: 5, 94: 3 F 94: 3 57: 1 57: 1, S 1000	19	., ,	 π,		4,	2: 3,	1, H	69: 1	1,1	8	∴ 	ž. 1,	o 	Ö …	o ai	4: 26			
AR061: 6, AR039: 5 L0439: 5, L0608: 4, L0005: 3, H0013: 3, L0759: 3, L0594: 3, H0329: 2, L0776: 2, S0001: 1, H0156: 1, L0157: 1, H0040: 1, H0264: 1, S0038: 1, H0100: 1, H0538: 1, L0769: 1, H0144: 1, H0547: 1, L0777: 1 and H0008: 1.	AR104: 19, AR033: 15,	AR039:	AR053:	AR052:	AR089:	H0052: 3, S0001: 2,	S0222: 1, H0194: 1, L0157:	, L0369: 1, L0769: 1	.0767: 1, L0794: 1, H0144:	and L0438: 1.	AR053:	AR096:	AR061:	AR104:	AR052:	S0184: 26 and S0186: 8			
<u>A L D W D H H H H H H</u>	⋖	≪_	<u>∢</u>	<u>∢</u>	<u>∢</u>	_	<u> S</u>	<u>-</u>	1	+	⋖	<u>∢</u>	_<	_∢	_∀				
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	1465								•		1466	٠		_					
	208						-				1	·							
	65 - 508										151	498							
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	13									1	32								
	597213										597832								
	B31										E55								
	HCENB31										H7TME55								
	50 H								=	-	-								
	10	-]	51		_						

80-111	<i>-11</i>	100-116, 14-30
	,	
AR060: 18, AR055: 16, AR104: 14, AR061: 14, AR033: 11, AR089: 11, AR039: 7, AR096: 6, AR053: 5, AR052: 4 L0439: 13, L0438: 6, H0052: 3, H0009: 2, L0769: 2, L0794: 2, L0741: 2, H0229: 1, H0572: 1, H0569: 1, L0770: 1, L0796: 1, L5566: 1, L0805: 1, L0789: 1 and L0786: 1.	AR096: 5, AR055: 3, AR039: 2, AR061: 2, AR033: 2, AR089: 2, AR104: 2, AR052: 2, AR060: 1, AR053: 1 S0038: 1	AR033: 10, AR055: 9, AR104: 6, AR052: 5, AR089: 5, AR096: 5, AR060: 5, AR061: 4, AR053: 4, AR039: 2 L0757: 13, L0759: 7, L0747: 6, T0010: 5, L0748: 5, L0770: 4, L0764: 4, L0750: 4, H0031: 3, L0438: 3, L0756: 3, L0758: 3, H0013: 2, S0010: 2, H0135:
1467 Ser-15 to His-22, Pro-46 to Pro-52, Gly-63 to Ser-69, Arg-111 to Ser-116, Pro-121 to Asn-129, Ala-136 to Gly-145.		Thr-8 to Glu-13, Thr-89 to Leu-96.
1467	1468	1469
75 - 539	18 - 362	472
62	89	4
600734	610609	613240
HDHMA49 600734	HBXBG68	HGBFC53
52	53	54

2, L0598; 2, L076; 1; 2, L0546; 2, L0775; 2, L0806; 2, L0776; 2, L0806; 2, L0776; 2, L0806; 2, L0777; 2, L0879; 2, L0659; 2, L0659; 2, L0659; 1, L0622; 1, H0222; 1, H0222; 1, H0222; 1, H0222; 1, H0222; 1, H0222; 1, H0232; 1, L0455; 1, H0232; 1, L0455; 1, L0732; 1, L0532; 1, L0646; 1, L0652; 1, L0652; 1, L0652; 1, L0652; 1, L0652; 1, L0653; 1, L0652; 1, L0653; 1, L0652; 1, L0653; 1, L
2. L0598; 2, L0766; 2, L0776; 2, L0646; 2, L0776; 2, L0766; 2, L0776; 2, L0665; 2, L0776; 2, L0657; 2, L0689; 2, L0665; 1, L0689; 2, L0685; 1, L0689; 2, L0685; 1, L0682; 2, L0685; 1, L0682; 1, L0682; 1, L0682; 1, L0682; 1, L0688; 1, L0689; 1, L06
2, L0598: 2, L076: 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,
2, L0588; 2, L0766; 2, L0765; 2, L0646; 2, L0765; 2, L0657; 2, L0659; 2, L0666; 2, S0328; 2, L0439; 2, L0777; 2, L0777; 2, L0731; 2, L0592; 2, L0362; 2, H0026; 1, H0556; 1, H0556; 1, H0029; 1, L0005; 1, S0348; 1, H0038; 1, H0048; 1, H0048; 1, H00497; 1, H0319; 1, H00497; 1, H0039; 1, H0156; 1, H0075; 1, H0079; 1, H0139; 1, H0052; 1, H0079; 1, H0048; 1, H0052; 1, H0048; 1, H0049; 1, H0049; 1, H0049; 1, L0495; 1, H0049; 1, L0495; 1, H0049; 1, L0495; 1, L0495; 1, L0495; 1, L0495; 1, L0658; 1, L0678; 1, L0658; 1, L0678; 1, L
2, L0598; 2, L0765; 2, L0775; 2, L0686; 2, L0776; 2, L0686; 2, L0776; 2, L0687; 2, L0689; 2, L0689; 2, L0689; 2, L0689; 2, L0689; 2, L0777; 2, L0777; 2, L0731; 2, L0592; 2, L0362; 2, H0265; 1, H0256; 1, H0228; 1, H0288; 1, S0488; 1, H0058; 1, H0058; 1, H0058; 1, H00497; 1, H03497; 1, H03499; 1, H04497; 1, H0048; 1, L0489; 1, H0048; 1, L0489; 1, H0048; 1, L0049; 1, H0048; 1, L0049; 1, H0048; 1, L0049; 1, L00
2, 10588; 2, 10761; 2, 1,0666; 2, 10775; 2, 1,0806; 2, 10776; 2, 1,0806; 2, 1,0776; 2, 1,0806; 2, 1,0775; 2, 1,0839; 2, 1,0439; 2, 1,0666; 2, 80328; 2, 1,0439; 2, 1,06058; 1, 1,00058; 1,00059; 1,000
2, L0598: 2, L0766: 2, L0775: 2, L0646: 2, L0766: 2, L0666: 2, L0777: 2, L0659: 2, L0666: 2, S0328: 2, L0439: 2, L0652: 1, L0653: 1, L0656: 1, L0653: 1, L0658: 1, L06
2, L0598; 2, L0761; 2, L0666; 2, L0776; 2, L0666; 2, L0308; 2, L0776; 2, L0687; 2, L0666; 2, S0328; 2, L0439; 2, L0777; 2, L0322; 2, L0439; 2, L0777; 2, L0362; 2, L0392; 2, L0362; 1, H0232; 1, S0348; 1, L0008; 1, S0358; 1, S0358; 1, S0358; 1, S0358; 1, S0358; 1, S0358; 1, H0569; 1, S0358; 1, H0569; 1, H0569; 1, H0569; 1, H0579; 1, H0331; 1, H0581; 1, H0581; 1, H0581; 1, H0581; 1, H0039; 1, H0178; 1, H0123; 1, S0050; 1, H0123; 1, S0050; 1, H0123; 1, L0455; 1, H0316; 1, H0039; 1, L0455; 1, H0316; 1, H0039; 1, L0459; 1, L0459; 1, L0464; 1, H0036; 1, L0459; 1, L0464; 1, H0036; 1, L0469; 1, L0662; 1, L0659; 1, L0659; 1, L0659; 1, L0659; 1, L0659; 1, L0658; 1, L0658; 1, L0858; 1, L0788; 1, L0658; 1, L0588; 1, L0788; 1, L0658; 1, L0588; 1, L0788; 1, L0658; 1, L0588; 1, L0788; 1, L0788; 1, L0658; 1, L0588; 1, L0788; 1, L07
2, L0598: 2, L0761: 2, L0646: 2, L0776: 2, L0665: 2, L0776: 2, L0667: 2, L0698: 2, L0698: 2, L0667: 2, L0698: 2, L0698: 1, L0697: 2, L0392: 1, L0322: 1, S0418 1, L0008: 1, S0468: 1, H0028: 1, S0468: 1, H0028: 1, S0468: 1, H0018: 1, S0468: 1, H0018: 1, L0668: 1, L0668: 1, L0668: 1, L0668: 1, L0668: 1, L0688: 1, L0688: 1, L0688: 1, L0768: 1, L0688: 1, L06888: 1, L06888: 1, L0
2, 10598; 2, 10761; 2, 10646; 2, 10766; 2, 10766; 2, 10767; 2, 10667; 2, 10777; 2, 10667; 2, 10777; 2, 10777; 2, 10777; 2, 10771; 2, 10731; 2, 1, 2, 10328; 1, 10032; 1, 10032; 1, 10032; 1, 10036; 1, 10048; 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
2, L0598: 2, L076: L0646: 2, L0766: 2, L0866: 2, L0766: 2, L0865. 2, L0777: 2, L0877: 2, L0659: 2, L0731: 2, L0322: 2, L0431: L0703: 1, L0005: 1, S003-1, L0005: 1, S003-1, L0005: 1, S003-1, L0009: 1, H063-1, L045-1, H063-1, L065-1, L065-1, L086-1, L086-1
2, L0598: 2, L0646: 2, LC 2, L0806: 2, L0657: 2, LC 2, S0328: 2, L0777: 2, LC 2, L0362: 2, L0777: 2, LC 2, L0362: 2, H0556: 1, H 1, L0005: 1, S0358: 1, S0 1, S046: 1, S 1, H0497: 1, H0497: 1, H0497: 1, H0581: 1, H0014: 1, H 1, H0123: 1, L0351: 1, LC 1, L0662: 1, L0662: 1, L0655: 1, L0655: 1, L0655: 1, L0655: 1, L0655: 1, L0658: 1, LC
2, 1059 1, 10646: 2, 1080 1, 10807: 2, 1080 1, 10807: 2, 1086 1, 10808: 3, 3038: 3, 3038: 3, 3038: 3, 4038: 3, 4039: 4, 40138: 4, 40032: 4, 40032: 4, 40032: 4, 40032: 4, 40032: 4, 40032: 4, 40035:

	107-139	61- <i>97</i>	21-42, 44- 66
1, L0809: 1, L0543: 1, L0647: 1, L0665: 1, H0698: 1, S0374: 1, H0520: 1, H0689: 1, H0682: 1, H0521: 1, S0028: 1, L0742: 1, L0740: 1, L0751: 1, L0749: 1, L0752: 1, S0031: 1, H0445: 1, L0596: 1, L0588: 1, L0593: 1, L0603: 1, H0667: 1 and H0542: 1.	AR055: 8, AR060: 5, AR061: 4, AR089: 4, AR033: 4, AR096: 4, AR039: 3, AR053: 3, AR104: 2, AR052: 2 L0754: 7, H0644: 4, H0031: 2, L0748: 1, L0747: 1 and H0543: 1.	AR055: 7, AR061: 6, AR060: 5, AR096: 4, AR033: 4, AR052: 3, AR089: 3, AR053: 3, AR104: 2, AR039: 2 H0575: 4, H0271: 3, H0250: 1 and L0599: 1.	AR033: 7, AR060: 4, AR096: 3, AR089: 3, AR053: 3, AR061: 3, AR052: 2, AR055: 1,
	Thr-91 to Pro-97.	Ala-15 to Glu-26, Lys-33 to Ser-47, Cys-53 to Thr-60, Cys-119 to Trp-127.	Thr-10 to Ala-20, Asp-82 to Asn-102.
·	1470	1471	1472
	336 - 767	5 - 478	129 - 434
	9	99	<i>L</i> 9
	613734	613777	614169
	HPMCK47	HAPNX53	HOFAE02
	55	56	57

WO 01/90304		
,	143-159	78-96
	· · · · · · · · · · · · · · · · · · ·	
0 2, H0692: 1, H0619: 1, S0010: 1, H0264:	1. 5, 4, 3, 3, 1 1 10583: 00761:	3, 3, 4
AR104: 1, AR039: 0 S0136: 7, S0356: 2, S0410: 2, H0486: 2, H0672: 2, H0170: 1, H0657: 1, H0692: 1, H0254: 1, H0402: 1, H0305: 1, S0358: 1, H0619: 1, L0717: 1, H0406: 1, H0415: 1, H0599: 1, S0010: 1, T0115: 1, H0545: 1, S0051: 1, H0617: 1, H0264: 1, H0100: 1, L0659: 1, L0789: 1, L0665: 1, H0519: L0789: 1, L0665: 1, H0519:	AR052: 1 and H0352: 1. AR055: 5, AR033: 5, AR060: 4, AR104: 4, AR052: 3, AR061: 3, AR096: 2, AR039: 1 L0439: 6, L0438: 3, L0809: 2, L0748: 2, H0583: 1, S0001: 1, T0010: 1, L0456: 1, H0598: 1, L0761: 1, L0783: 1, S0028: 1, L0749: 1, L0756: 1, S0458:	1 and H0352: 1. AR039: 6, AR053: AR052: 3, AR033: AR096: 3, AR055:
AR104: S0136: 7 2, H0486; H0170: 1 1, H0254; H0305: 1, 1, L0717: H0415: 1, 1, T0115: S0051: 1, 1, H0100; L0789: 1,	H0422: 1 AR055: AR060: AR053: AR052: AR096: L0439: (L0809: 2, 1, S0001: L0456: 1, 1, L0783: L0749: 1,	1 and H0352: 1 AR039: 6, AR AR052: 3, AR AR096: 3, AR
		Ser-19 to Val-24, Pro-35 to Asn-42, Pro-44 to Gly-59,
	1473	1474
	16 - 525	234 -
	89	69
	614801	615231
	HSLIQ83	HNTMD04
	28	59

	92-111, 45-61	90-76	48-81, 126-156, 89-115, 21-38, 1- 17, 180-
·			
AR089: 3, AR060: 2, AR061: 2, AR104: 2 L0755: 3, H0521: 2, L0754: 2, L0747: 2, S0003: 1, L0369: 1, L0667: 1, L0659: 1, L0647: 1, L0790: 1, L0663: 1, L0664: 1, H0520: 1, H0518: 1, S0152: 1, S0404: 1, H0436: 1, L0748: 1 and H0423: 1.	AR104: 20, AR096: 11, AR089: 8, AR033: 7, AR052: 5, AR060: 5, AR053: 5, AR039: 4, AR055: 2, AR061: 1 H0599: 1, H0555: 1 and S0390: 1.	AR055: 12, AR089: 8, AR033: 8, AR061: 7, AR060: 7, AR053: 5, AR052: 5, AR096: 4, AR039: 1, AR104: 0 L0758: 2, H0339: 1, L0664: 1 and L0731: 1.	AR096: 1, AR089: 1, AR104: 1, AR033: 0, AR052: 0, AR061: 0, AR039: 0, AR060: 0, AR055: 0, AR053: 0
Gly-96 to Gly-101.	Thr-17 to Ser-28, Ser-39 to Gly-45.	Arg-5 to Glu-10.	Glu-121 to Asp-128. AR096: 1, AR089: AR104: 1, AR033: AR052: 0, AR061: AR039: 0, AR060: AR055: 0, AR053:
	1475	1476	1477
	47 - 379	345 - 680	748
•	70	71	72
	616154	616652	618715
	HRABY48	HDDAA17	HTRAC41
	9	61	62

196, 161- 177 52-68, 26- 42 130-146 130-146 50	
S0001: 2, H0730: 2, L0581: 2, H0713: 1, H0735: 1, H0164: 1 and S0028: 1. AR039: 25, AR055: 11, AR039: 25, AR053: 10, AR096: 9, AR060: 9, AR104: 8, AR061: 6 S0003: 1, L0498: 1 and L0599: 1. AR055: 10, AR052: 9, AR055: 10, AR052: 9, AR055: 4, AR061: 4, AR089: 6, AR060: 6, AR096: 4, AR061: 4, AR096: 4, AR061: 1, AR096: 1, AR099: 1, AR053: 1, AR104: 1, AR053: 1, AR104: 1, AR055: 0, AR052: 0 L0755: 3, S0003: 2, H0521: 2, S0470: 1, S0354: 1, S0444: 1, S0360: 1, S0046: 1, H0574: 1,	H0051: 1, H0553: 1, H0646: 1, S0210: 1, H0529: 1,
Lu-94 to Trp-102, Al Arg-78 to Glu-84, Al Leu-94 to Trp-102, Al Lys-113 to Thr-118. Al A	H(
1478	
57 - 407 1 - 519 221 - 670	
73 74 75	
620219	
HOSCV06 HEMFC09	

	57-73	79-95
L0662: 1, H0659: 1, H0658: 1, H0539: 1, H0436: 1, L0758: 1, L0599: 1, S0192: 1, S0276: 1 and H0423: 1.	AR053: 3, AR052: 3, AR096: 2, AR033: 2, AR055: 2, AR089: 2, AR104: 1, AR061: 1, AR104: 1, AR039: 0 L0748: 4, L0749: 3, H0529: 2, L0439: 2, H0624: 1, T0002: 1, H0295: 1, H0638: 1, H0619: 1, H0013: 1, H0581: 1, H0263: 1, H0457: 1, H0561: 1, H0538: 1, L0500: 1, L0646: 1, L0794: 1, L0664: 1, H0547: 1, H0690: 1, H0435: 1, H0696: 1, S0044: 1, L0779: 1, L0752: 1, L0596: 1, L0485: 1, L0593: 1 and S0384: 1.	AR096: 2, AR055: 2, AR089: 1, AR104: 1, AR061: 0, AR033: 0, AR060: 0, AR052: 0,
	Glu-90 to Asn-95, Arg-101 to Lys-108.	Ala-25 to Phe-44.
	1481	1482
		272 - 571
	76	77
	625432	625517
	HNTRJ16	HKAEJ09
	99	67

W U 01/90304			
	56-72, 18- 34	46-64	50-70, 20- 42
): 0 1, and	2; 5, 3, 2; 3, 4; 1, 7; 1, 7; 1, 1, 1, 1, 1, 2, 1, 1, 2, 1, 1, 2, 1, 1, 2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	: 1, : 1, : 0,	က်က်က်လ် — :: မ :: မ ::
AR039: 0, AR053: 0 H0083: 1, H0494: 1, L0776: 1, L0744: 1 and L0777: 1.	7 9 - 8 - 6 -	.R096: 2, AR089: R039: 1, AR033: R061: 1, AR104: R060: 0, AR052: R055: 0	.R055: 6, AR061: .R052: 3, AR060: .R096: 3, AR033: .R053: 2, AR104: .R039: 2, AR104: .H0040: 3
AR039: H0083: L0776: 1 L0777: 1		<u> </u>	4444
	Tyr-49 to Arg-55.	Pro-13 to His-18, Pro-20 to Lys-27, Ala-29 to Pro-47, Lys-69 to Arg-75, Ser-77 to Ser-85.	1485 Phe-42 to Tyr-50.
	1483	1484	1485
	22 - 414	92 - 517	44 - 361
	78	79	80
	625566	625622	626178
	HKMMS65	HNHGE09	HTTCT34
	89	69	70

7-27, 114- 130, 88- 104, 31- 47, 61-77	86-105, 12-29, 55- 71
Arg-133 to Lys-145.	AR096: 35, AR089: 31, AR104: 25, AR060: 17, AR033: 16, AR052: 15, AR039: 14, AR053: 13, AR055: 10, AR061: 6 H0556: 3, H0208: 3, H0050: 3, L0471: 3, H0179: 3, H0644: 3, S0344: 3, H0521: 3, L0439: 3, S0420: 2, S0360: 2, H0619: 2, H0599: 2, H0264: 2, H0280: 2, S0210: 2, H0547: 2, H0658: 2, L0750: 2, L0731: 2, L0588: 2, L0604: 2, H0543: 2, H0265: 1, T0002:
1486	1487
751 - 1185	354 - 722
	83
637714	638175
HBIAS14 637714	HLHSC60
71	72

	136-153, 18-34
1, H0140: 1, S0114: 1, H0341: 1, S0001: 1, H0669: 1, H0662: 1, H0306: 1, S0418: 1, S0408: 1, H0580: 1, L0717: 1, H0549: 1, H0453: 1, H0592: 1, H0497: 1, H0632: 1, T0039: 1, H0172: 1, H0575: 1, H0620: 1, H0039: 1, H0575: 1, H0648: 1, H0024: 1, H0615: 1, H0124: 1, H0615: 1, H0124: 1, H0615: 1, H0124: 1, H0615: 1, H0124: 1, H0646: 1, H059: 1, H0646: 1, H0538: 1, L0646: 1, H0538: 1, L0646: 1, L0789: 1, L0663: 1, L0438: 1, H0520: 1, H0519: 1, S0126: 1, H0689: 1, H0651: 1, H0539: 1, S0152: 1, S0028: 1, L0748: 1, L0777: 1, L0753: 1, H0343: 1, L0591: 1, L0592: 1, L0591: 1, L0592: 1, H0506: 1, H0612: 1,	AR055: 17, AR033: 17, AR052: 13, AR061: 13,
	Gln-7 to Arg-12, Pro-69 to Glu-76,
	1488
	427 - 894
	83
	638229
	H6ESA95
·	73

																									_			
R060: 11,	R096: 4	126: 4,	18: 3, H0551:	0559: 2,	522: 2, H0617:	0382: 2,	38: 2, H0670:	0605: 2,	24: 1, H0225:	0657: 1,	(41: 1, H0306:	0418: 1,	54: 1, S0046:	10592: 1,	257: 1, H0491:	10635: 1,	253: 1, H0318:	10123: 1,	.35: 1, H0038:	10087: 1,	46: 1, L0369:	0772: 1,	42: 1, L0764:	0363: 1,	94: 1, L0766:	0806: 1,	59: 1, L0809:	0664: 1,
Leu-119 to Trp-125. AR053: 11, AR060: 11,	AR039: 5, AF	H0556: 7, S0126: 4,	S0360: 3, H0618: 3, H0551:	3, S0132: 2, H0559: 2,	H0545: 2, H0622: 2, H0617:	2, H0413: 2, L0382: 2,	L0665: 2, L0438: 2, H0670:	2, S3014: 2, L0605: 2,	L0591: 2, H02;	1, S0114: 1, H0657: 1,	H0656: 1, H03	1, H0638: 1, S0418: 1,	S0442: 1, S0354: 1, S0046:	1, H0392: 1, H0592: 1,	H0587: 1, H0257: 1, H0491:	1, H0013: 1, H	H0575: 1, H0253: 1, H0318:	1, H0569: 1, H0123: 1,	H0083: 1, H0135: 1, H0038:	1, H0040: 1, H0087: 1	S0440: 1, H0646: 1, L0369:	1, L0769: 1, L0	L0646: 1, L0642: 1, L0764:	1, L0773: 1, L0363:	L0768: 1, L0794: 1, L0766:	1, L0803: 1, LC	L0653: 1, L0659: 1, L0809:	1, L0663: 1, L0664:
Leu-119																												
																				-								
																		···										

HOG9: 1, HO435: 1, HO436: 206, AR06:			
HKMAA36 638339 84 169- 1489 Lys-126 to Phe-135, AR104: 504, AR061: 378, AR1-135 to Ala-168, AR060: 336, AR065: 226, Thr-185 to Val-196, AR039: 171, AR039: 122, AR069: 171, AR099: 173, AR099: 173, AR099: 171, AR099: 173, AR099: 173, AR099: 173, AR099: 174, AR		78-112, 1-36, 49-77, 213-232, 105-121, 29-45	191-207, 139-155
HKMAA36 638339 84 169- 1489 Lys-126 to Phe-135, 888 Thr-185 to Val-196, Thr-185 to Val-196, Thr-185 to Val-196, 1489 Lys-25 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to In-137, Pro-128 to Ile-137, Pro-128 to Ile-137.			
HKMAA36 638339 84 169- 1489 Lys-126 to Phe-135, 888 Thr-185 to Val-196, Thr-185 to Val-196, Thr-185 to Val-196, 1489 Lys-25 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to In-137, Pro-128 to Ile-137, Pro-128 to Ile-137.			
HKMAA36 638339 84 169- 1489 Lys-126 to Phe-135, 888 Thr-185 to Val-196, Thr-185 to Val-196, Thr-185 to Val-196, 1489 Lys-25 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to In-137, Pro-128 to Ile-137, Pro-128 to Ile-137.			
HKMAA36 638339 84 169- 1489 Lys-126 to Phe-135, 888 Thr-185 to Val-196, Thr-185 to Val-196, Thr-185 to Val-196, 1489 Lys-25 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to In-137, Pro-128 to Ile-137, Pro-128 to Ile-137.	H0436: 1, H0445: 1,	: 378, : 296, : 173, : 122, : 94 9, H0593: 3, S0434: 2, S0360: 1, S0015: 1, H0672:	1, 1, 1,
HKMAA36 638339 84 169- 1489 Lys-126 to Phe-135, 888 Thr-185 to Val-196, Thr-185 to Val-196, Thr-185 to Val-196, 1489 Lys-25 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to In-137, Pro-128 to Ile-137, Pro-128 to Ile-137.	H0435: 1, 1, L0750: 1, L0757: 1, 1, H0653: 1, H0653:	4, AR061 6, AR055 3, AR039 1, AR052 1, AR096 4, H0494: 80442: 6, 7, S0408: 2, H0059: 3, 1, H0292: 1, H0292: 1, H0673: 1, 1, H0647: 1, G6689: 1, 803406:	2, AR052: 1, AR055: 1, AR104: 1, AR061:
HKMAA36 638339 84 169- 1489 Lys-126 to Phe-135, 888 Thr-185 to Val-196, Thr-185 to Val-196, Thr-185 to Val-196, 1489 Lys-25 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to Thr-16, Thr-23 to His-28, 1490 Lys-5 to In-137, Pro-128 to Ile-137, Pro-128 to Ile-137.	10691: 1, 1 1, H0478: 20731: 1, 1 1, L0601: 1	NR104: 50 NR060: 33 NR033: 20 NR089: 17 NR053: 10 S0358: 11 S0354: 7, S N, H0616: 7, H0616: 2, S H0484: 1, H0642: 1 H042: 1, H0642: 1, H0662: 1, H	
HKMAA36 638339 84 169- 1489 888 888 888 888 888 888 888 888 888			, 121, 7.
HKMAA36 638339 84 169- 1489 888 888 888 888 888 888 888 888 888		ys-126 to P Nsn-153 to A Thr-185 to V	ys-5 to Thr- hr-23 to His ily-111 to L ro-128 to Ile
HKMAA36 638339 84 HLTFA02 638553 85		<u> </u>	
HKMAA36 638339 HKTFA02 638553		169 - 888	259 - 996
HKMAA36		48	85
		638339	638553
77		HKMAA36	HLTFA02
		47	75

	180-210,	257-282,	326-349,	116-134,	308-325,	12-28
			-			
vo &						
AR060: 1, AR053: 0 L0747: 6, L0766: 4, L0749: 4, L0362: 4, H0046: 3, L0666: 3, S0126: 3, S0132: 2, H0013: 2, L0758: 2, L0596: 2, H0624: 1, H0341: 1, S0001: 1, S0360: 1, S0408: 1, S0278: 1, H0370: 1, T0114: 1, H0083: 1, H0553: 1, H0606: 1, H0561: 1, H0641: 1, S0142: 1, L0520: 1, L0641: 1, L0764: 1, L0805: 1, L0526: 1, L0664: 1, H0702: 1, H0659: 1, H0696: 1, S0406: 1, R0666: 1, S0330: 1, H0539: 1, H0696: 1, S0406: 1, S3014: 1, S0027: 1, L0777: 1, L0755: 1, L0731: 1, L0759: 1, H0422: 1 and S0452: 1.	AR060: 6, AR096: 5,	AR089: 5, AR052: 5,	AR053: 3, AR033: 3,	AR055: 1, AR061: 1,	AR104: 1, AR039: 0	H0539: 8, H0046: 3,
A l u l c s s s s s s s s s s s s s s s s s s		Lys-64 to Leu-71, A		Pro-102 to Trp-110, A	Tyr-162 to Cys-169, A	Asp-367 to Ala-377.
	1491					
	48 -	1193				
	98					
	645267					
	HISBE12		_ -			
	9/					

	19-51, 100-116, 120-136, 41-57	117-133
~	ė · · ·	
H0039: 2, H0553: 2, H0090: 2, L0750: 2, L0605: 2, S0282: 1, H0431: 1, H0036: 1, H0421: 1, H0196: 1, T0003: 1, S6028: 1, H0252: 1, H0031: 1, H0111: 1, H0591: 1, H0412: 1, T0068: 1, S0044: 1, L0752: 1, H0445: 1 and L0581: 1.	AR104: 44, AR033: 31, AR061: 18, AR060: 15, AR055: 14, AR039: 12, AR089: 12, AR096: 10, AR053: 9, AR052: 6 S0007: 3, H0038: 2, S0344: 2, L0750: 2, T0002: 1, H0125: 1, S0420: 1, S0358: 1, S046: 1, H0411: 1, S0278: 1, H0085: 1, H0545: 1, H0031: 1, H0182: 1, H0646: 1, H0134: 1, S0031: 1, L0591: 1, H0423: 1 and H0422: 1.	AR053: 51, AR052: 50, AR089: 25, AR055: 25, AR033: 17, AR061: 14, AR060: 12, AR096: 12, AR104: 1, AR039: 0
	Glu-9 to Arg-15, Pro-71 to Lys-79.	Met-1 to Val-12.
	0 1492	1493
	62 - 520	158 -
	8	88
	645268	655007
	HEBAE43	HSBBC07
	12	78

WO 01/90304

78-95, 1-	17, 52-68							89-107								23-68, 23-	41									131-151,	7000
AR055: 10, AR060: 9,	AR096: 8, AR053: 8,	8, AR089:	_	H0131: 2, S0002: 2,	H0664: 1, H0586: 1, H0574:	1, H0563: 1, H0028: 1 and	S0428: 1.	AR052: 30, AR053: 25,	AR096: 23, AR055: 18,	AR089: 16, AR060: 12,	AR033: 10, AR061: 8,	AR104: 6, AR039: 5	L0756: 2, H0170: 1,	H0441: 1, S0051: 1, T0010:	1, H0436: 1 and L0779: 1.	AR055: 44, AR039: 39,	AR053: 24, AR033: 20,	AR052: 18, AR089: 17,	AR104: 16, AR096: 14,	AR060: 13, AR061: 12	L0748: 5, L0157: 3,	L0777: 2, H0549: 1, H0617:	1, L0638: 1, L0774: 1,	L0775: 1, H0144: 1 and	L0755: 1.	AR039: 8, AR033: 5,	1 700ct 4 7 C20ct 4
1494 Pro-16 to Lys-21.								Val-7 to Met-23,	Leu-41 to Lys-46.							Asp-14 to Leu-22.										1497 Gln-18 to Tyr-24,	ָרָלָיִי בְּיִייִּיִּיִי בְּיִייִּיִּיִי בְּיִייִּיִי בְּיִיִּיִּיִי בְּיִייִּיִּיִי בְּיִייִּיִּיִי בְּיִייִי
								1495					, _			1496										1497	_
18 - 329								344 - 18								51 - 395										228 -	()
68								96						-		91										92	
655590								656211								656288			 	·						656815	
HL2AE73								HE20057								HEEAR13						-				HFIYL13	
79								80								81										82	

50	46-62
AR082: 4, AR104: 4, AR089: 4, AR055: 3, AR060: 3, AR061: 3 L0766: 3, H0413: 2, L0794: 2, H0659: 2, H0591: 1, T0042: 1, H0494: 1, L0769: 1, L0667: 1, L0800: 1, L062: 1, L078: 1, L0755: 1, L0731: 1, L0758: 1, H0444: 1, S0242: 1 and H0542: 1.	AR096: 17, AR033: 20, AR096: 17, AR033: 16, AR089: 14, AR055: 11, AR060: 11, AR061: 8 L0754: 9, L0780: 3, L0755: 3, L0591: 3, S0196: 3, H0255: 2, H0306: 2, H0041: 2, H0553: 2, H0674: 2, H0521: 2, L0748: 2, L0779: 2, L0758: 2, L0779: 2, L0758: 2, S0298: 1, H0346: 1, S0360: 1, S0408: 1, H0549: 1, H0550: 1, H0485: 1, H0428: 1, H0628: 1, L0369: 1, L0769: 1, L0761: 1, L0800: 1,
	1498
	542
	33
	658066
,	HLWBH14
	83

01/20304		1 € 17 € 50 17 10
	52-74, 34- 50, 75-91	47-64
L0803: 1, L0782: 1, L0791: 1, L0532: 1, L0777: 1, H0444: 1, L0596: 1, S0026: 1 and H0653: 1.	AR033: 7, AR053: 4, AR055: 4, AR052: 3, AR096: 3, AR089: 3, AR039: 2, AR104: 1 L0766: 4, L0758: 4, L0646: 2, L0805: 2, H0670: 2, L0745: 2, L0756: 2, L0759: 2, H0351: 1, H0156: 1, H0328: 1, H0652: 1, L0520: 1, L0771: 1, L0648: 1, L0748: 1, L0774: 1, L0438: 1, L0439: 1, L0740: 1, L0747: 1 and S0412: 1.	AR052: 29, AR053: 25, AR096: 23, AR089: 12, AR055: 8, AR033: 6, AR104: 0, AR060: 4, AR104: 0, AR039: 0 L0805: 25, L0157: 7, L0776: 7, S0474: 5, L0731: 5, H0457: 4, L0748: 4, L0747: 4, S0278: 3, H0538: 3, S0404: 3, S0476: 2, H0619: 2, H0009: 2, H0529:
	4444 HUHHHH	1500 Phe-68 to Ser-77, A Lys-79 to Thr-90, A Cys-107 to Leu-114, A Pro-116 to Trp-121, A Pro-124 to Asn-133. A LL L
	1499	1500
	- 879 - 878	22 - 444
	8	95
	659283	659380
	HATDW51	69ОмФО
	84	85
		·

	252-268, 133-149, 106-122
2, L0662: 2, L0803: 2, L0774: 2, L0439: 2, L0751: 2, H0170: 1, H0713: 1, H0716: 1, H0295: 1, H0341: 1, S0001: 1, H0663: 1, H0306: 1, H0402: 1, S0418: 1, L0005: 1, S0222: 1, H0587: 1, T0060: 1, H0427: 1, H0575: 1, T0048: 1, H0674: 1, S0038: 1, H0620: 1, S0388: 1, H0628: 1, H0561: 1, S0036: 1, H0488: 1, H0412: 1, S0038: 1, H0561: 1, L0598: 1, L0770: 1, L0769: 1, L0794: 1, L0804: 1, L0775: 1, L0655: 1, L0809: 1, L0775: 1, L0663: 1, H0520: 1, H0689: 1, H0670: 1, S0380: 1, H0521: 1, H0522: 1, S0027: 1, L0754: 1, L0779: 1, L0777: 1, H0522: 1, S0194: 1, H0423: 1 and H0352: 1.	AR053: 1, AR055: 1, AR060: 1, AR033: 1, AR096: 0, AR061: 0,
	Pro-8 to Ala-14, Glu-68 to Gln-75, Gln-80 to Glu-85,
•	231 - 1501 1058
	96
	659801
	HNTBM67
	98

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o,	,	200	JUUUS: /, LUGOS: /, LUGSY: ; I 0666: 6 H0547: 6	., L2006: 9, IX3777: 0, .0740: 6. S6028: 4. L0483:	→	L0756: 4, L0779: 4, S0194:		L0646: 3, L0521: 3, L0663:	3,	H0696: 3, L0439: 3, L0777:	4	S0356: 2, S0442: 2, S0354:	~\$	H0046: 2, H0563: 2, L0471	~î	H0040: 2, H0623: 2, S0440:	oî.	.0641: 2, L0771: 2, L0768:	2, L0774: 2, L0805: 2,	.056	4	H0660: 2, H0648: 2, H0672:	~5	L0731: 2, L0758: 2, S0031:	ວໂ	S0026: 2, S0196: 2, H0170:	1,	H0717: 1, H0381: 1, S0212
352:			7.7	4:	754: 7	.4,5	88:3	: 3, I	135: (9:3,	171:	2,8	08: 2	3:2,	399	3: 2,	20:2	: 2, I	305: 2	: 2, 1	670:	8: 2,	51: 2	: 2, 5	95: 2	: 2, F	585:	1: 1,
0, AR052: 0,	(S0222: 8, L0662: 8,	LUUUS: /, LUBBS: /, LU 6 I 0666: 6 H0547: 6	6028	4, L0438: 4, L0754: 4,	2770	, S03	0521	3, L0664: 3, H0435: 3,	043	3, H0624: 2, H0171: 2,	0442	2, S0360: 2, S0408: 2,	4056	2, S0051: 2, H0266: 2,	1062	2, L0598: 2, L0520: 2,	.077	, 108	0518	2, H0519: 2, H0670: 2,	1064	2, S0028: 2, L0751: 2,	0758	, L05	0196	1, H0686: 1, H0685: 1,	4038
9.	⊙ , ⊙ ,	., . , . , .	, ', 'E	9.5	38:4	: 4, I	49:3	: 3, I	64:3	3, I	24: 2	: 2, S	60:2	. 2, I	51:2	: 2, F	98: 2	: 2, L	74: 2	: 2, L	19:2	: 2, F	28: 2	2, T	96: 2	2, S	86: 1	: 1, F
R089	AR039:	S022	25 I	45	27	0756	S00	9646	, L06	9690	H06	0356	S03	0046	S00	9	L05	0641	107	9770	H05	0990	S00	0731	105	3026	H06	0717
Ala-170 to Leu-178. AR089:	<u>∢</u>		<u>1 v</u>	<u> </u>	4		4.		<u> </u>	프	<u> </u>	Ø	<u> </u>	프	<u> </u>	프	<u>Q</u>	H	<u>Q</u>	그	<u>6</u>	王	<u> </u>	ı	-Q	<u>x</u>	<u>–</u>	H
3u-17																			•									
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-170														,		,												
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<u>-</u>	58-75
1, H0662: 1, S0418: 1, S0376: 1, S0045: 1, S0046: 1, H0411: 1, H0369: 1, H0550: 1, H0438: 1, H0602: 1, T0040: 1, H0013: 1, H0427: 1, S0280: 1, H0590: 1, H0390: 1, S0474: 1, H0178: 1, H0178: 1, H0562: 1, H0178: 1, H0373: 1, H0201: 1, H0355: 1, S0003: 1, H0013: 1, H0355: 1, S0003: 1, H0013: 1, H0551: 1, H0553: 1, L0370: 1, S0370: 1, S0450: 1, L0560: 1, L0637: 1, L0650: 1, L0637: 1, L0653: 1, L0753: 1, L0755: 1, L0753: 1, L0753: 1, L0755: 1, L0753: 1, L07	1 and S0242: 1. AR055: 31, AR060: 21,
	Met-1 to Lys-7,
	37 - 537 1502
	660532 97
	87 HAIDY03

		44-72, 69-
558: 558: 559: 559: 559: 555: 696:	192:	
AR033: 20, AR061: 13, AR089: 13, AR053: 12, AR089: 13, AR053: 12, AR056: 6, AR039: 4 L0766: 5, L0803: 3, L0748: 3, L0748: 3, L0740: 3, L0758: 2, L0771: 2, L0809: 2, L0665: 2, S0330: 2, L0750: 2, L0756: 2, L0731: 2, L0759: 2, L0756: 2, L0731: 1, S0420: 1, S0420: 1, H0638: 1, H0510: 1, H0416: 1, H0687: 1, H0591: 1, L0763: 1, L0769: 1, H0659: 1, H0658: 1, H0690: 1, H0658: 1, L0749: 1, H0690: 1, H0658: 1, L0749: 1,	1, 2007	3 AR053: 3
	L0747: 1 and H	1503 Thr-107 to Asn-114 AR096:
Pro-9 to Ser-19, Pro-30 to Ser-38, Arg-89 to Glu-95, Leu-105 to Trp-113, Lys-124 to Thr-129.		Thr-107 to Asn
		<u> </u>
		35 - 375
		80
		661/136
		HNPHO19
		88

85, 13-29	179-199	50-70
.72:	.05: 59: 36:	
2, AR060: 2, 1, AR052: 1, 1, AR104: 1, 0, AR039: 0 8, L0755: 2, H0341: 1, S02 : 1, L0800: 1, S0216: 1 and	6, AR033: 4, 3, AR052: 3, 3, AR089: 3, 3, AR089: 3, 2, AR104: 0, 7, L0750: 6, 1, L0779: 4, L08: 1, L0747: 2, L077: 1, S0010: 1, H0622: 1, S00: 1, 1, L0803: 1, 1, L0803: 1, 1, S3014: 1, L0758: 1.	3, AR053: 3, 2, AR096: 2, 2, AR039: 2, 2, AR033: 2, 1, AR061: 1 8, L0744: 7,
AR033: 2, AR060: 2, AR089: 1, AR052: 1, AR055: 1, AR104: 1, AR061: 0, AR039: 0 H0693: 8, L0755: 2, L0731: 2, H0341: 1, S0222: 1, L0769: 1, L0800: 1, L0665: 1, S0216: 1 and H0521: 1.		AR089: 3, AR053: AR052: 2, AR096: AR104: 2, AR039: AR055: 2, AR033: AR060: 1, AR061: H0651: 8, L0744: 7
AAAA J - J H	AAAAA I I AAAA I I I II I	4444
·	Pro-29 to Lys-34, Ser-91 to Thr-97.	1505 Val-4 to Thr-11, Ile-15 to Asn-20, Arg-35 to Lys-44.
	1504	1505
	51 - 860	85 - 480
	66	100
	661694	662513
	HAGBC45	HNTNT65
	68	06

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																												_	
												_						••											
360:		H0638: 2, H0052: 2, H0123:		H0615: 2, H0039: 2, H0424:		H0059: 2, L0659: 2, L0519:		43:		.0589: 2, H0656: 1, H0662:	1, S0420: 1, S0358: 1,	222:		.0021: 1, H0544: 1, H0546:		H0012: 1, H0266: 1, H0188:		H0292: 1, H0252: 1, H0673:		302:		L0662: 1, L0650: 1, L0774:		793:		H0520: 1, H0658: 1, H0672:		H0436: 1, S0037: 1, L0747:	
, SO	6	, HC	<u></u>	光 ,		3,	ર્ભ	5	4	, HO	_ ,	, SO.	Ţ,	, HO	-	, H	: 1;	Ħ,	- -	SO,	1,	S,	1,	5	Ļ,	H,		Ĭ,	1,
L0748: 6, H0620: 4, S0360:	755	52: 2	2, H0083: 2, H0328: 2,	39:2	2, H0163: 2, H0040: 2,	9:2	378:	4.2	758	6: 1	358:	7:1	280	4.1	l, H0545: 1, H0081: 1,	56: 1	1, H0687: 1, H0288: 1	52: 1	, S0036: 1, H0100: 1,	4.	643	0:1	805	3: 1	1, L0665: 1, S0053:	58: 1	1, H0522: 1, S0406:	7:1	, L0749: 1, L0779: 1,
1062	J,	, 100 100	?, H(100), H(965	; S0	301	, 10	1065	, SO	1063	1, S0	1054	l, H(1020	l, H(102	, H0	3014	, LO	265	, L0	.078	, S0	90E	l, S0	3003	, 10
6,1	1 2: 3	., 2,	83: 2	2,	63: 7	2,	38: 2	2,5	50:2	2, <u>F</u>	<u>%</u>	1, F	74:	1, F	45:]	<u></u>	87:]	<u>.</u>	36: 1	1,5	51: 1	1, I	75: 1	1, I	55: 1	1,1	72:	1,5	1 9: 1
748	S012	638	00H	615	HOI	059	26.	012:	L07.	589:	S04 2	408:	H05	021:	H05	012	90H	292	S003	42	Ĕ	662:	L63,	776:	8	520	H05	436	L07
<u>3</u>	<u>ش</u>	H	બ	丑	ત્યું	呈	Q,	S 3	9	<u> </u>	<u>_</u>	8		2	1,	丑	<u></u>	丑	1,	H	1,	<u>고</u>	<u>, </u>	<u> </u>	<u>_</u>	Ħ		呈	7,
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															_														

	8-35, 38-	56, 59-75												45-69, 76-	101, 115-	131										41-57	
	•	121014,	142470,	156225,	164200,	164200,	601316,	601410,	601757					108730,	147781,	172471,	186580,	264800,	266600,	278760,	600760,	600760,	600761.	600761.	602066		
	6q22.1-22.3													16p12-p13.1 108730,													
L0731: 1, S0031: 1, S0434: 1 and L0366: 1.	AR096: 6, AR052: 4,	AR060: 4, AR055: 4,	AR033: 4, AR039: 4,	AR104: 3, AR089: 3,	AR053: 3, AR061: 3	L0766: 4, L0748: 4,	L0747: 4, L0752: 3, L0759:	3, S0212: 1, S0356: 1,	H0574: 1, L0105: 1, H0188:	1, H0040: 1, L0772: 1,	L0774: 1, S0328: 1, L0749:	1, L0755: 1, L0596: 1 and	H0667: 1.	AR033: 8, AR053: 5,		AR060: 4, AR096: 4,	AR055: 3, AR104: 3,	AR061: 3, AR039: 1	L0439: 4, L0418: 1,	S0010: 1, L0455: 1, S0028:	1 and L0741: 1.					1508 Glu-98 to Gln-106. AR089: 28, AR039: 26, AR096: 25, AR052: 16,	
	Asn-87 to Asn-92.													1507 Pro-27 to Ala-37.												Glu-98 to Gln-106.	
	1506													1507												1508	
	825 -	1148										•		102 -	512			·								112 - 543	
	101													102												103	
	665234													666416											•	666429	
	HTTAA50													HAGBX32												HHTMM1 8	
	91													6												93	

	48-64	123-139
AR053: 14, AR060: 14, AR033: 12, AR104: 12, AR061: 3, AR055: 3	AR052: 3, AR053: 3, AR052: 3, AR053: 3, AR104: 1, AR096: 1, AR061: 1, AR096: 1, AR089: 1, AR039: 0 S0422: 7, L0748: 6, L0664: 4, H0581: 3, L0665: 3, H0038: 2, H0659: 2, L0743: 2, L0751: 2, S0434: 2, L0596: 2, L0592: 2, L0411: 1, H0556: 1, H0222: 1, H0656: 1, S0116: 1, S0358: 1, S0376: 1, S0444: 1, S0360: 1, S0132: 1, S0476: 1, H0591: 1, H0040: 1, S0142: 1, S0002: 1, L0643: 1, L0662: 1, L0794: 1, L0766: 1, L0791: 1, H0547: 1, H0519: 1, H0518: 1, H0521: 1, L0749: 1, L0777: 1 and H0422: 1.	AR036: 1, AR060: 0, AR033: 0, AR061: 0,
	Ser-14 to Arg-20, Pro-92 to Ala-97, Glu-104 to His-110.	Ala-62 to Glu-74.
	1509	1510
	296 - 625	26 - 469
	104	105
	627779	668286
	HHFGR08	HHBEU19
	46	95

	59-75, 1- 17, 104- 120, 169- 185	370-406, 10-38, 430-456, 262-279, 338-354, 303-320, 232-250, 476-492, 105-121, 180-196	54-71
AR055: 0, AR089: 0, AR053: 0, AR104: 0, AR052: 0, AR039: 0 H0036: 1, L0471: 1, H0373: 1, L0804: 1 and H0665: 1.	Tyr-35 to Gln-42, AR096: 7, AR053: 5, Asp-141 to Gly-160. AR052: 3, AR104: 3, AR089: 3, AR104: 3, AR061: 1, AR055: 0 H0580: 1, T0042: 1, S0002: 1 and L0439: 1.	Arg-54 to Trp-62, AR033: 8, AR055: 7, Pro-68 to Ile-77, AR060: 6, AR089: 4, Asn-124 to Ala-130, AR052: 4, AR061: 3, Arg-155 to Lys-161, AR096: 3, AR053: 2, Ser-166 to Glu-178, AR104: 1, AR039: 1 Ile-407 to Ser-413, H0561: 2, H0539: 2, S0276: Pro-494 to Met-507, H0561: 2, H0539: 2, S0276: Pro-510 to Asp-516: 2, H0294: 1, S0212: 1, S0132: 1, H0431: 1, S0005: 1, H0544: 1, H0123: 1, H0566: 1, H0547: 1, H0569: 1, R0546: 1, H0555: 1 and S0242: 1.	AR096: 4, AR089: 2, AR053: 2, AR052: 2,
	1511	1512	1513
	34 - 627	246 - 1880	10 - 618
	106	107	108
	670586	672653	675380
	HWBBB21	HAIDX85	HMMAV0 6
	96	26	86

	79-104	59-75, 84- 100, 23-39
	AR033: 3, AR104: 2, AR096: 2, AR053: 2, AR059: 1, AR089: 1, AR052: 1, AR060: 1, AR061: 1, AR055: 0 L0769: 3, L0747: 3, L0759: 3, L0783: 2, L0438: 2, H0539: 2, L0439: 2, L0758: 2, L0589: 2, L0717: 1, L0598: 1, L0520: 1, L0794: 1, L0375: 1, H0144: 1 and L0779: 1.	AR053: 52, AR052: 44, AR055: 40, AR104: 28, AR033: 28, AR089: 27, AR060: 23, AR061: 22,
	lle-52 to Ser-59, Arg-106 to Asn-111, Gln-122 to Lys-130.	Pro-13 to Arg-23.
	1514	1515
·	291 - 680	408 -
	109	110
	677920	678316
	HISAM25	HRODX93
·	66	100

WO 01/	903																										.,	430
·	137-155,	1-19																					_					
																									·:		-	
AR096: 22, AR039: 20 H0052: 1 and H0598: 1.	· ·	(1	AR053: 1, AR061: 1,	AR055: 1, AR096: 0,	AR039: 0	L0748: 11, L0749: 9,	S0408: 6, S0002: 4, L0776:	4, H0521: 4, L0777: 4,	S0436: 4, L0588: 4, H0638:	3, S0358: 3, H0575: 3,	L0646: 3, S0126: 3, L0758:	3, L0596: 3, H0543: 3,	S0282: 2, S0354: 2, S0444:	2, S0360: 2, S0476: 2,	T0110: 2, H0046: 2, S0003:	2, L0483: 2, T0042: 2,	S0150: 2, S0422: 2, L0763:	2, L0772: 2, L0766: 2,	L0803: 2, L0783: 2, L0665:	2, L0438: 2, H0659: 2,	S0152: 2, H0704: 2, L0779:	2, L0731: 2, L0759: 2,	S0434: 2, L0591: 2, L0599:	2, H0653: 2, H0685: 1,	H0583: 1, H0657: 1, H0656:	1, S0116: 1, S0001: 1,	H0483: 1, S0442: 1, S0376:	1, S0468: 1, H0619: 1,
	Asp-23 to Glu-28,	Ser-49 to Pro-54,	Glu-61 to Thr-67,	Glu-72 to Asp-81,	Glu-83 to Asp-118,	Gly-156 to Arg-162,	Asp-184 to Tyr-205,		Gln-273 to Asp-278,		Phe-333 to Ser-338,	Lys-351 to Arg-357,	Gly-367 to Asp-375,	Asn-399 to Glu-414,	Gln-424 to Arg-443,	Glu-447 to Glu-457,	Arg-462 to Lys-476,	Lys-485 to Phe-492.	•									
	1516																											
	238 -	1713																										
	111											•																
	678819																											
	HLJDK82																											
	101											·																

	73-90, 12-
H0393: 1, S0278: 1, H0549: 1, H0574: 1, H0075: 1, H0599: 1, H0036: 1, H0590: 1, S0010: 1, H0251: 1, T0115: 1, H0830: 1, H0572: 1, L0471: 1, H0014: 1, H0169: 1, H0708: 1, H0063: 1, H0628: 1, L0055: 1, H0623: 1, H0708: 1, H0063: 1, H0488: 1, H0413: 1, H0646: 1, L0769: 1, L0637: 1, L0648: 1, L0773: 1, L0665: 1, L0773: 1, L0655: 1, L0659: 1, L0526: 1, L0809: 1, L0790: 1, L0665: 1, L0669: 1, L0790: 1, L0666: 1, L0663: 1, S0374: 1, H0435: 1, H0670: 1, H0672: 1, R0435: 1, L0756: 1, L0752: 1, S0031: 1, S0013: 1, S0432: 1, L0608: 1, L0362: 1, S0026: 1, H0667: 1, S0026: 1, H0667: 1, S0026: 1, H0667: 1, S00242: 1, S0196: 1, H0542: 1, H0423: 1,	H0422: 1 and S0424: 1. AR033: 5, AR089: 4,
	1517
	164
	112
	682668
,	HCFMJ37
	102

82	87-105, 31-47
	14, 112, 110, 9, 7 0123: 0123: 0028: 0059: 10428: 0763: 0763:
3, AR096: 3 3, AR053: 2 1, AR061: 1 0	AR055: 15, AR039: 14, AR089: 12, AR083: 11, AR060: 10, AR053: 9, AR061: 9, AR104: 8, AR096: 7 H0666: 13, H0620: 7, H0666: 13, H0620: 7, L0740: 5, L0747: 6, L0659: 7, L0740: 5, L0750: 5, L0757: 5, S0360: 4, H0123: 4, L0748: 4, L0777: 4, L0748: 4, L0777: 4, L0748: 4, L0777: 4, L0388: 4, S0420: 3, S0358: 4, H0208: 3, H0545: 3, H0246: 2, H0252: 2, H0251: 2, H0628: 2, H0551: 2, L0770: 2, L0774: 2, L0770: 2, L0772: 2, L0755: 2, L0753: 2, L0753: 2, L0751: 2, L0752: 2, L0755: L0751: 2, L0752: 2, L0753: L0753
AR060: 3, AR052: 3, AR055: 1, AR104: 0 H0423: 1	AR055: 15, AR039: 14, AR089: 12, AR052: 12, AR033: 11, AR060: 10, AR053: 9, AR061: 9, AR104: 8, AR096: 7 H0666: 13, H0620: 7, L0731: 7, L0747: 6, L0659: 5, L0740: 5, L0750: 5, L0757: 5, S0360: 4, H0123: 4, S0022: 4, H0135: 4, L0666: 4, L0665: 4, S0028: 4, L0748: 4, L0777: 4, L0588: 4, S0420: 3, S0358: 3, H0208: 3, H0545: 3, H0046: 3, H0592: 2, H0544: 2, H0024: 2, H0551: 2, H0100: 2, S0210: 2, L0763: 2, L0770: 2, L0774: 2, L0661: 2, L0518: 2, H0547: 2, H0670: 2, S0037: 2, L0661: 2, L0752: 2, L0755:
4	
	·
	1518
532	373 - 26
	113
	682949
	HMWAP1
	103

SULPANDERS (1, 10048; 1, 10048; 1, 10048; 1, 10049; 1, 10048; 1, 10049; 1, 10048; 1, 10049; 1, 10048; 1, 10049; 1, 10048; 1, 10049; 1, 10048; 1, 10049; 1, 10048; 1, 1					 					
S0194.2, H0170.1, H0265. 1, H0686.1, 50040.1, H0329.1, H0441.1, H0638.1, 1, 50444.1, H0538.1, H0329.1, S0468.1, S0046.1, 1, 50142.1, H0445.1, L0717.1, 1, 50142.1, H0445.1, L0717.1, 1, H0586.1, H033.1, L0717.1, 1, H0586.1, H033.1, L0717.1, 1, H0586.1, H0041.1, 1, H0575.1, H063.1, H0041.1, 1, H053.1, H0051.1, 1, H0634.1, H0631.1, 1, H0634.1, L0772.1, 1, L0662.1, L0772.1, 1, L0662.1, L0776.1, 1, L0662.1, L0778.1, 1, L0662.1, L0778.1, 1, L0662.1, L0789.1, 1, L0663.1, L0789.1, 1, L0663.1, L0789.1, 1, L0631.1, L0789.1, 1, L0631.1, H0632.1, H0637.1, 1, H0639.1, L0778.1, L0599.1, 1, L0639.1, L0778.1, L0789.1, 1, L0639.1, L0778.1, L0789.1, 1, L0639.1, L0789.1,										
S0194.2, H0170: I, H0565: I, H0361: I, H0565: I, H0365: I, H0341: I, H0341: I, H0341: I, H0341: I, H0341: I, S0040: I, S0446: I, S0046: I, S0132: I, S0468: I, S0046: I, S0132: I, S0468: I, S0046: I, H0329: I, H0329: I, H0645: I, L0717: I, S0132: I, H0645: I, H0341: I, H0553: I, H0645: I, H0331: I, L0021: I, H0052: I, H0331: I, L0021: I, H0052: I, H0331: I, H0641: I, H0651: I, H0651: I, H0641: I, H0642: I, L0764: I, L0767: I, L0662: I, L0773: I, L0662: I, H0652: I, L0773: I, L0663: I, H0652: I, L0778: I, L0663: I, H0652: I, L0778: I, L0663: I, H0652: I, L0778: I, L0663: I, L0778: I, L0778: I, L0778: I, L0663: I, L0778:										
S0194: 2, H0170; 1, H0265: 1, 1, H0686: 1, S0040; 1, H00295: 1, H00295: 1, H0034: 1, H0038: 1, H00395: 1, S0044: 1, H0038: 1, S0044: 1, H0039: 1, S0044: 1, H0039: 1, S0044: 1, H0039: 1, S0046: 1, S0132: 1, S0046: 1, S0132: 1, S0046: 1, S0132: 1, S0132: 1, S0132: 1, L0011: 1, H0039: 1, L0043: 1, L0048: 1, L0048: 1, L00773: 1, L0062: 1, L0076: 1, L0066: 1, L0076: 1, L0066: 1, L0078: 1, L0069: 1, L0078: 1, L0069: 1, L0078: 1, L0069: 1, L0078: 1,										
S0194-2, H.0055. 1, H0086. I, S0040. I, H00295. I, H0344. I, H0038. I, S0444. I, H0580. I, H00239. I, S0468. I, S0046. I, H00239. I, S0468. I, S0046. I, H00329. I, S0478. I, H0550. I, H0058. I, H0051. I, H0058. I, H0053. I, L0021. I, H0058. I, H0053. I, H0041. I, H0058. I, H0058. I, H0059. I, H0051. I, H0061. I, H0050. I, L0163. I, H0051. I, H0051. I, L0163. I, H0051. I, L0063. I, L0761. I, L0063. I, L0761. I, L0663. I, L0781. I, L0809. I, L0663. I, L0783. I, L0809. I, L0663. I, H0682. I, H0683. I, H0059. I, L0783. I, L0809. I, L0631. I, H0682. I, H0687. I, H0059. I, L0781. I, L0693. I, L0782. I, H0059. I, L0781. I, L0693. I, L0782. I, H0059. I, L0783. I, L0789. I, L0693. I, L0789. I, L0789. I, L0693. I, L0789. I, L0693. I, L0789. I, L0693. I, L										
S0194 2, H0170: 1, H0265: 1, H0686: 1, S0040: 1, H0289: 1, H0329: 1, H0341: 1, H0341: 1, H0329: 1, S0448: 1, S0146: 1, S0132: 1, S0446: 1, S0132: 1, S0468: 1, S0146: 1, S0132: 1, S0468: 1, L0717: 1, S0132: 1, S0476: 1, H0550: 1, H0550: 1, H0550: 1, H0578: 1, H0550: 1, H0052: 1, H0053: 1, H0053: 1, H0053: 1, H0053: 1, H0053: 1, H0051: 1, H0653: 1, H0051: 1, H0653: 1, H0051: 1, H0653: 1, H0051: 1, H0653: 1, H0653: 1, L0767: 1, L0662: 1, L0772: 1, L0772: 1, L0662: 1, L0772: 1, L0772: 1, L0662: 1, L0772: 1, L0772: 1, L0662: 1, L0772:		·						<u> </u>		
80194. 2, H0170. 1, H0265. 1, H0686. 1, S0040. 1, H0295. 1, H0341. 1, H0638. 1, S0444. 1, H0381. 1, H0381. 1, H0329. 1, S0448. 1, S0046. 1, S0132. 1, S0448. 1, S0046. 1, S0132. 1, S048. 1, S0046. 1, S0132. 1, H0341. 1, L0717. 1, S0278. 1, H0545. 1, L0717. 1, H0562. 1, H0581. 1, H0052. 1, H01631. 1, H0041. 1, H0645. 1, L0763. 1, H0054. 1, H0163. 1, H0631. 1, H0054. 1, L0763. 1, L0763. 1, L0665. 1, L0776. 1, L0656. 1, L0776. 1, L0656. 1, L0778. 1, L0689. 1, H0709. 1, S0152. 1, H0627. 1, H0709. 1, S0152. 1, H0627. 1, H0709. 1, S0152. 1, H0627. 1, L0639. 1, L0776. 1, L0659. 1, H0669. 1, L0776. 1, L0639. 1, L0778. 1, L0739. 1, L0639. 1, L0778. 1, L0739. 1, L0639. 1, L0748. 1, L0748. 1, L0748. 1, L0748. 1, L0639. 1, L0648.										
S. 1. 10686: 1, 80040: 1, 1, 10686: 1, 80040: 1, 1, 10686: 1, 80040: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,										
S01942 2 H0170: 1 H0686 1, H0686: 1, S0040: 1, H0686: 1, S0040: 1, H0632: 1, S0448: 1, S0040: 1, H06132: 1, S0448: 1, S0040: 1, H06132: 1, S0476: 1, H06132: 1, S0476: 1, H06132: 1, S0476: 1, H06132: 1, S0476: 1, H06132: 1, H0632: 1, H0633: 1, H0632: 1, H0633: 1, H0633: 1, H0633: 1, H0633: 1, H0633: 1, H0633: 1, H0632: 1, H0633: 1, L0763: 1, L0763: 1, L0776: 1, L0643: 1, L0776: 1, L07776: 1,	.;; <u> </u>	.; .;			;;			4.	-:-	
Supple: 2, 1, 10686: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	, 1026 1063	0046	, 1, H004	l, 1005	F, H063	, 0806 0806	,	, 1068 1,	1062	, , , ,
2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	01: 2 7: 1, F 140: 1 1: 1, I	. 1, S : 1, S 76: 1 5: 1, 1	553: 253: 3: 1, 1	381: 1, H	F. 1, 1	: 1, L 67: 1 : 1, L	76: 1 : 1, I	89: 1 3: 1, 1	: 1, F 27: 1	: 1, I 61: 1
S0194. 2, 1070. 2, 2019. 2, 1, 10686. 1 1, 10686. 1, 1, 10686. 1, 1, 10632. 1, 2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	0170 0170 0170 , S00 1034]	864 804 804 804 804	1033 1033 1015 1015	, HOC 0163	, 1103 1033 107	0643 L07 0651	L07 0783	L07 20682 H00	0152 S00	0745 L03
2, 1, 20. 1, 1006. 1, 1006. 1, 1007. 1, 1007. 1, 1006. 1, 1006.	28: 7, H,	. 1, S, 1, 5, 1, 5, 1, 5, 1, 5, 1, 5, 1, 1, 5, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	0. 1, 1, H 75: 1 1, H	53: 1 1, L	1, H 46: 1	1, 13, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	5: 1, 1, L	13: 1, 1, H 59: 1	1, S	1, L 73: 1,
	194: 194: H06 295:	S013 S013 S013 S013	302/ 3586: H05' 3052:	H0500050000000000000000000000000000000	H06)800: 1.06()775:	L08(L054 1663: 1106:	1709	1059:
	^{2, 2, ±} ± −	<u> </u>	<u>, </u>	<u>- H -</u>	<u>, H</u> ;	<u>3 4 3</u>	<u> </u>	<u>-, 5 -</u>	<u>, H +</u>	3-15
				<u></u>						
									<u>.</u>	
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	92-120,	30-50, 61-	7.7																									
1 and H0667: 1.	AR055: 25, AR052: 25, AR053: 22, AR033: 18,		AR096: 15, AR039: 15,	AR061: 14, AR104: 14	L0758: 7, L0766: 5,	L0558: 5, L0750: 5, S0360:	4, S0410: 4, L0747: 4,	S0007: 3, S0438: 3, L0763:	3, L0769: 3, L0775: 3,	S0380: 3, S0404: 3, L0748:	3, L0754: 3, L0749: 3,	L0759: 3, H0423: 3, H0661:	2, S0132: 2, H0441: 2,	H0494: 2, L0506: 2, L0761:	2, L0554: 2, L0523: 2,	L0776: 2, L0526: 2, L0532:	2, L0665: 2, S0126: 2,	S0378: 2, H0522: 2, L0742:	2, L0752: 2, L0731: 2,	L0757: 2, S0040: 1, H0717:	1, H0294: 1, S0134: 1,	H0657: 1, H0381: 1, H0341:	1, H0483: 1, H0669: 1,	H0638: 1, S0358: 1, S0444:	1, S0408: 1, H0208: 1,	H0351: 1, S0278: 1, H0392:	1, H0333: 1, L0622: 1,	H0486: 1, T0039: 1, L0021:
	Ala-4 to Phe-9, Thr-155 to Asn-162.																											
	9 1519								•		_																	
	34 - 519																											
	114										_														···			
	684293																											
	HMCFA76											•																
	104																											

H0570: 1, H0086: 1, L0471:			
HU150: 1, H0073: 1, A010: 1, H0010:		176 143	292-308, 292-308, 90-106, 252-268
HTHCM28 684309 115 145 - 1520 Pro-29 to Asn-35, AR061: 1, 10055: 1, 10058: 1, 10068: 1, 100471: 1, 10068:		106300	108300, 108800, 120290, 120290
HTHCM28 684309 115 145 - 1520 Pro-29 to Asn-35, 1392 Val-184 to Arg-191, Thr-219 to Thr-225, Ala-273 to Ser-281,			6777do
HTHCM28 684309 115 145 - 1520	1, H0575: 1, S0010: 1, H0150: 1, H0086: 1, L0471 1, H0012: 1, H0083: 1, H0688: 1, H0181: 1, H0617 1, H0673: 1, S0364: 1, H0068: 1, S0366: 1, H0376: 1, H0163: 1, H0038: 1, H0616: 1, H0063: 1, H0087 1, H0059: 1, H0280: 1, L0475: 1, H0633: 1, H0646: 1, S0144: 1, S0344: 1, H0529: 1, L0762: 1, L0639: 1, L0662: 1, L0767: 1,	1, L0378; 1, L0527; 1, L0657; 1, L0540; 1, L0546; 1, L0518; 1, L0783; 1, L0663; 1, S0052; 1, H0669; 1, H0660; 1, H0660; 1, H0660; 1, H0670; 1, H0660; 1, L0777; 1, L0755; 1, H0444; 1, H0445; 1, H0667; 1, H0543; 1 and H0422; 1, L0565; 1,	
HTHCM28 684309 115 145 - 152		Dr. 70 to A cr. 25	Tro-29 to Asn-53, Val-184 to Arg-191, Thr-219 to Thr-225, Ala-273 to Ser-281
HTHCM28 684309 115		1530	0261
		341	1392
HTHCM28		-1.	CII
		00000	084309
	,	OCACATA	HI HCMZ8

164-180	
120810, 120820, 142857, 142858, 150270, 167250, 177900, 177900, 201910, 233100, 235200, 235550, 256550,	600261, 601868, 602280, 602475
	.: 5. 1. 5: 7:
AR104: 5, AR039: 4 L0748: 10, H0457: 5, L0758: 4, L0776: 3, L0790: 3, L0665: 3, H0617: 2, L0803: 2, L0655: 2, H0658: 2, L0744: 2, L0747: 2, L0588: 2, L0604: 2, H0265: 1, H0583: 1, S0116: 1, S0212: 1, S0442: 1, S0132: 1, H0351: 1, H0369: 1, H0441: 1, H0013: 1, S0010: 1, H0377: 1, H0046: 1, H0361: 1, R0366: 1, H0135: 1, H0510: 1, H0040: 1, H0063: 1, H0477: 1, H0059: H0063: 1, H0649: 1	1, 10152. 1, 1103-2. 1, 1, L0772: 1, L0769: 1, L0372: 1, L0771: 1, L0766: 1, 1, L0677: 1, L0806: 1, L0805: 1, L0679: 1, L0666: 1, L0663: 1, L0438: 1, H0593: 1, 1, L0438: 1, H0648: 1, H0651: 1, S0330: 1, S0380: 1, 1, S0330: 1, L0751: 1, L0756: 1, L0731: 1, L0596: 1, 1, S0026: 1, S0276: 1 and
Gly-319 to Glu-327, Gly-339 to Ser-345, Thr-358 to Gly-363, I Lys-410 to Phe-416.	
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	70-86						47-66,	275-291,	146-162,	99-115															
	112410, 113520,	135700,	186940,	186940,	200990,	960209																			
	12p12																								
H0423: 1.	6, AR096: 4, AR053:	AR104: 3, AR052: 3,	AR055: 2, AR060: 3, AR055: 2, AR061: 2	H0170: 1, H0484: 1,	S0360: 1, H0309: 1, H0040:	1, L0611: 1, L0596: 1, H0542: 1 and H0543: 1	AR060: 5, AR052: 5,	AR089: 4, AR053: 4,	AR096: 3, AR055: 3,	AR033: 2, AR039: 2,	AR061: 2, AR104: 1	L0779: 4, S0360: 3,	L0803: 3, L0747: 3, L0758:	3, S0354: 2, H0637: 2,	S0422: 2, L0646: 2, L0519:	2, L0665: 2, H0436: 2,	L0750: 2, H0657: 1, S0007:	l, S6016: 1, H0415: 1,	H0486: 1, H0069: 1, H0427:	I, S0280: 1, H0118: 1,	H0014: 1, S0214: 1, H0328:	l, H0615: 1, H0553: 1,	H0628: 1, S0440: 1, H0529:	1, L0766: 1, L0650: 1,	L0775: 1, L0776: 1, L0655:
		His-140 to Pro-148.								7	-7.												<u> </u>		
	1521						1522																		
	180 - 623						75 - 965					_				_									
	116						117																		
	685054						685191														_			-	
	HHEDB45				_		HTACX15												•					_	
	106						107			_					. —.										

1, H0658: 2: 1, 3: 1, 4: L0485: 5: 1, 5: 1, 6: 0, 7: 1, 11 L0803: 11
1, H0658: 1, H0658: 1, L0485: 1, L0485: 2, 1, 4: 1, 11, L0803: 1, L0803: 1, L07069: 1, 5, 1, 4, H0124: 2, 3, 3, L0774: 3, L0774: 3, L0774: 3, L0774:
1, H0658: 1, L0485: 1, L0485: 1, L0485: 2, 1, 4: 1, 4: 1, 1, L0803: 1, L0803: 1, Lond 1, L0803: 2, 1, 1, L0803: 2, 1, 1, L0803: 2, 1, 2, 1, 3, L0774: 3, L0774: 3, L0774: 3, L0774:
2: 1, 10658: 1, 1, 10485: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
1, L0783: 1, L0809: 1, S0374: 1, H0693: 1, H0658: 1, L0745: 1, L0752: 1, L0731: 1, L0757: 1, L0485: 1 and H0422: 1. AR089: 2, AR039: 1, AR053: 1, AR104: 1, AR053: 1, AR104: 1, AR053: 0, AR061: 0, AR053: 0, AR061: 0, AR054: 1, H0112: 1, L0803: 1, H0660: 1, S0330: 1, L0748: 1, L0747: 1 and S0242: 1. AR089: 8, AR055: 7, AR039: 6, AR033: 6, AR052: 6, AR060: 6, AR052: 5, AR104: 4 L0747: 14, L0439: 11, L0747: 14, L0439: 11, L0749: 5, H0251: 4, H0124: 4, H0052: 3, H0545: 3, L0770: 3, L0804: 3, L0774: 3, L0776: 3, L0659: 3, L0663: 3, H0547: 3, L0748:
Pro-89 to Gly-96, Gly-119 to Leu-125, Thr-135 to Pro-141, Thr-160 to Arg-170, Glu-189 to Glu-196, Asp-229 to Asp-236, Arg-278 to His-286, Asp-337 to Tyr-348.
1523
324 - 713 24 - 1067
118
685340
108 HFIZN55

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S0436: 3, H0341: 2, S0476:	2, H0318: 2, H0083: 2,	H0591: 2, H0264: 2, L0648:	L0803: 2, L0665: 2,	L0779: 2, L0595: 2, S0011:	2, H0556: 1, H0717: 1,	S0442: 1, S0360: 1, T0008:	H0329: 1, S0045: 1,	S0278: 1, S0222: 1, H0643:	l, H0156: 1, H0575: 1,	H0706: 1, H0390: 1, H0196:	H0085: 1, H0041: 1,	H0123: 1, H0081: 1, L0471:	H0011: 1, H0014: 1,	H0373: 1, H0510: 1, H0687:	1, H0288: 1, S0022: 1,	1615: 1, T0023: 1, H0031	S0036: 1, H0038: 1,	H0100: 1, T0041: 1, H0560:	1, S0438: 1, S0440: 1,	344: 1, L0640: 1, L0371	1, L0796: 1, L0646: 1,	.0764: 1, L0773: 1, L0662:	1, L0363: 1, L0364: 1,	650: 1, L0775: 1, L0784	, L0806: 1, L0655: 1,	.0606: 1, L0526: 1, L0782:	1, L0783: 1, L4501: 1,	.0666: 1, L0664: 1, S0374:	1, S0148: 1, S0126: 1,
08	ζί.	DH	7	<u>a</u>	2	SO	1,	OS SO	<u>—</u>	HC	<u> </u>	HC		H	1)H	1	H	1,	0S	1	<u>21</u>	<u></u>	<u>1</u>	1,	<u>3</u>	<u>—</u>	2	1,
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	103-123, 143-160	62-78, 105-121
4 . 58:	3: 7: 7: 7: 7:	
H0683: 1, H0659: 1, H0658: 1, H0670: 1, S0044: 1, H0187: 1, H0626: 1, S3014: 1, L0740: 1, L0751: 1, L0750: 1, L0786: 1, L0780: 1, L0759: 1, S0260: 1, L0591: 1, L0593: 1 and H0543: 1.	AR089: 0, AR096: 0, AR060: 0, AR060: 0, AR061: 0, AR104: 0, AR055: 0, AR052: 0, AR039: 0 L0517: 4, L0769: 3, L0776: 3, L0776: 3, L0776: 3, L0776: 1, R0421: 1, S0132: 1, H0550: 1, H0036: 1, L0764: 1, L0761: 1, L0764: 1, L0805: 1, L0659: 1, H0691: 1, H0519: 1, S0378: 1, H0636: 1, L0778: 1, L0755: 1, L0758: 1 and L0697: 1.	AR096: 4, AR055: 3, AR061: 3, AR060: 3, AR053: 3, AR052: 3,
		1526 Glu-10 to Thr-15, Arg-33 to Glu-38, Leu-54 to Gly-59,
	1525	1526
	256 - 735	1521 - 1096
	120	121
	685604	686533
	HNFIL36	HSKZB03
	110	111

																													102-122
				_																		•							
AR089: 2, AR033: 2,	AR104: 2, AR039: 0	S0126: 8, S0420: 6, L0757:	S0212: 4, L0777: 4,	H0662: 3, L0743: 3, L0608:	3, H0653: 3, H0667: 3,	H0546: 2, S0314: 2, H0551:	2, L0564: 2, L0764: 2,	.0666: 2, H0660: 2, S0027:	2, L0740: 2, L0754: 2,	.0759: 2, L0591: 2, L0595:	2, H0665: 2, S0180: 1,	H0661: 1, S0418: 1, S0356:	1, T0007: 1, T0039: 1,	0040: 1, T0114: 1, H0013:	I, L0021: 1, H0599: 1,	H0036: 1, H0083: 1, L0669:	1, S0318: 1, S0316: 1,	H0284: 1, H0286: 1, S0340:	1, S0250: 1, H0553: 1,	S0364: 1, H0413: 1, H0494:	l, S0150: 1, L0763: 1,	.0775: 1, L0776: 1, L0657:	1, L0790: 1, H0689: 1,	H0690: 1, H0658: 1, S3012:	1, S0037: 1, S3014: 1,	S0028: 1, L0780: 1, L0731:	1, H0668: 1, S0194: 1 and	S0196: 1.	AR039: 5, AR089: 3,
	Pro-123 to Thr-133. A		9	H	'n	ĬĬ.		<u></u>		<u></u>		H		<u> </u>		H	<u></u>	H	<u>—</u>	<u> S</u>	1,	<u></u>		H		<u>S</u>		<u>S</u>	Leu-27 to Ser-41.
																													2 12 - 416 1527
								•												•							-		26 688935 122
																													112 HNTMZ26

	36-70, 25- 41, 67-83
AR096: 3, AR052: 3, AR104: 2, AR060: 2, AR053: 1, AR061: 1, AR055: 1, AR033: 1 L0748: 5, H0519: 3, H0486: 2, H0179: 2, H0509: 2, H0521: 2, L0588: 2, L0595: 2, H0624: 1, H0650: 1, H0657: 1, H0656: 1, S0444: 1, H0580: 1, S0046: 1, H0013: 1, H0599: 1, S0474: 1, L0471: 1, H0266: 1, H0188: 1, H0533: 1, L0637: 1, H0539: 1, S0364: 1, H0633: 1, L0637: 1, H0539: 1, S0378: 1, L0602: 1, S0146: 1, S3014: 1, L0756: 1, L0759: 1, L0480: 1, L0596: 1, L0608: 1, S0026: 1, H0542: 1, H0543: 1 and H0560: 1.	AR096: 88, AR052: 86, AR053: 68, AR089: 63, AR060: 53, AR104: 44, AR033: 37, AR039: 36, AR061: 15, AR055: 10 S0053: 3, L0752: 3, L0794: 2, S0052: 2, H0660:
HH; C; S; S; S; HH;	1528 Gly-6 to Gly-14.
	6 689978 123 68 - 370
	113 HHENC76

	33-61	300-328, 1-21, 180- 196
2: 6:		×
2, S0152: 2, L0595: 2, H0543: 2, H0583: 1, H0346: 1, T0109: 1, L0767: 1, L0768: 1, H0521: 1, L0745: 1 and S0194: 1.	AR039: 31, AR033: 26, AR104: 25, AR053: 22, AR052: 19, AR055: 19, AR089: 14, AR060: 13, AR096: 11, AR061: 10 L0439: 3, L0438: 2, L0756: 2 and S0388: 1.	AR033: 29, AR104: 25, AR060: 22, AR096: 17, AR089: 16, AR052: 13, AR039: 11, AR055: 9, AR053: 8, AR061: 5 L0752: 30, L0754: 17, L0740: 16, H0521: 14, L0439: 14, L0766: 12, S0003: 11, S0214: 11, L0777: 10, S0002: 8, L0776: 8, L0748: 8, L0755: 8, S0360: 7, L0665: 7, L0757: 7, T0067: 6, S0440: 6, L0770: 6, L0666: 6, L0747: 6, L0774: 5, L0751: 5, S0222: 4, H0575: 4, H0622: 4, L0662: 4, L0775:
	Ser-25 to Lys-32, Glu-63 to Gly-68.	Gin-153 to Ser-163, Ser-172 to Glu-178, Ala-204 to Asp-210, Ile-222 to Ala-236, Lys-284 to Ser-291, Met-342 to Arg-348
	1529	1530
	427	1184
	124	125
	691490	695741
	HHSGJ30	невед09
	114	115

			
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		·	
		·	
598:	34: 586: 471: 040:	720: 183: 1406: 567:	212: 145: 409:
3, LO 3, LO 3, LO 13, LO 13, LO	; , , , , , , , , , , , , , , , , , , ,	2, 103 2, 107 3, 107 3, 107 2, 50, 50, 5, 107 3, 106 1, 500	k: 1, l, S02 l: 1, s00 l, S00
4, H0547: 4, S0126: 4, S0380: 4, L0750: 4, L0758: 4, S0436: 4, L0362: 4, H0638: 3, H0580: 3, L0598: 3, S0374: 3, H0710: 3, H0522: 3, H0555: 3, L0356: 3, L0756: 3, L0731: 3, L0756: 3, L0756: 3, L0731: 3, L0756: 3, L0756: 3, L0731: 3, L0756: 3, L07	2, S0376: 2, E0294: 3, S0134: 2, S0376: 2, S0046: 2, H0393: 2, S0278: 2, H0586: 2, H0421: 2, T0110: 2, L0471: 2, S6028: 2, S0022: 2, H0591: 2, H0551: 2, H0412: 2, H0551: 2, H0412: 2,	H0494: 2, S0422: 2, L0520: 2, L0764: 2, L0768: 2, L0655: 2, L0659: 2, L0763: 2, L0664: 2, L0438: 2, H0648: 2, H0672: 2, S0406: 2, S0028: 2, L0780: 2, L0588: 2, L0599: 2, H0667: 2, S0196: 2, H0624: 1, H0171: 1, H0265: 1, S0040:	1, H0713: 1, S0114: 1, L0811: 1, H0341: 1, S0212: 1, S0001: 1, H0661: 1, H0305: 1, S0418: 1, S0045: 1, S0132: 1, S0476: 1, H0619: 1, H0415: 1, H0409
7: 4, 3, 4, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	2, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 7, 100, 100, 100, 100, 100, 100, 100,	2, SO-2, SO-2, SO-2, SO-2, SO-2, LO6 2, HO 2, HO 2, HO 2, HO 3, LO5 1, LO5 1, HO 1, HO	3: 1, S 1, HO: 1, HO: 1, SO/ 1, SO/ 1, HO
1054 380: 4 30436 538: 3 30374 522: 3 50756	393: 3 393: 3 393: 3 1015(421: 3 86028 390: 3	494: 2764 20764 555: 2 548: 2 60028 888: 2 888: 2	1, H0713: 1, S0114: 1, L0811: 1, H0341: 1, S0212: 1, S0001: 1, H0661: 1, H0305: 1, S0418: 1, S0045: 1, S0132: 1, S0476: 1, H0619: 1, H0415: 1, H0409:
3, 8 1, 8 1, 8 1, 8 1, 8 1, 8	1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	1, F 1, S 1, S 1, S HO, HO, HO, HO, HO, HO, HO, HO, HO, HO,

	139-158, 110-126
1, H0438: 1, H0013: 1, S0010: 1, S0665: 1, S0474: 1, H0327: 1, H0046: 1, L0157: 1, S0051: 1, T0010: 1, H0266: 1, H0179: 1, H0615: 1, H0096: 1, H0031: 1, H0674: 1, H0163: 1, H0038: 1, H0569: 1, E0569: 1, E0669: 1, E06	AR033: 7, AR052: 6, AR104: 5, AR060: 5,
	Ala-8 to Ser-15, His-36 to Glu-44,
	1531
	26 - 499
	126
	698634
	HJKSC77
	116

					-																	
						-				<u>.</u>		•••				<u></u>					· · · · · ·	
1992	171:	784		156:			471:		328:	-	1440:		638:		804:)547:		136:		749:	
358: 8, L0777: 8, 779: 6, L0362: 6, L0	.0752: 5, L0775: 4, 803: 3, L0759: 3, H0	H0657: 2, S0222: 2,	.0809: 2, L0665: 2,	126: 2, L0740: 2, L0	20755: 2, L0758: 2,	1/0: 1, 50416: 1, 50 10632: 1, H0036: 1,	010: 1, S0346: 1, LO	H0014: 1, H0373: 1,	266: 1, S0334: 1, HC	H0316: 1, S0036: 1,	412: 1, H0202: 1, SC	50150: 1, H0646: 1,	422: 1, L0763: 1, L0	L0764: 1, L0773: 1,	662: 1, L0649: 1, L0	L0774: 1, L0666: 1,	144: 1, H0691: 1, H(H0519: 1, H0690: 1,	683: 1, H0660: 1, SC	S0404: 1, S0406: 1,	028: 1, L0754: 1, L0	, L0750: 1, L0731: 1,
	5, 1 L0;	2, I H0	2,1	OS	2,1		SOC	1,1	OH.	1,1	OH.	<u>1.</u>	OS_	1,1	OI.	<u>.,</u>	OH HO	1,1	OH HO	1,8	N N N N N N N N N N N N N N N N N N N	1,1
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			-							-										-		
	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766:	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171:	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 2, L0784:	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 2, L0784: 2, L0809: 2, L0665: 2,	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 2, L0784: 2, L0809: 2, L0665: 2, S0126: 2, L0740: 2, L0756:	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 2, L0784: 2, L0809: 2, L0665: 2, S0126: 2, L0756: 2, L0758: 2, L0755: 2, L0758: 2,	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 2, L0784: 2, L0809: 2, L0665: 2, S0126: 2, L0766: 2, L0755: 2, L0758: 2, H0170: 1, S0418: 1, S0360: 1, H0632: 1, H0036: 1,	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 2, L0784: 2, L0809: 2, L0665: 2, S0126: 2, L0740: 2, L0756: 2, L0755: 2, L0758: 2, H0170: 1, S0418: 1, S0360: 1, H0632: 1, H0036: 1, S0010: 1, S0346: 1, L0471:	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L076: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 2, L0784: 2, L0809: 2, L0665: 2, S0126: 2, L0756: 2, L0755: 2, L0756: 2, L0755: 2, L0758: 2, H0170: 1, S0418: 1, S0360: 1, H0632: 1, H0036: 1, S0010: 1, S0346: 1, L0471: 1, H0014: 1, H0373: 1,	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 2, L0784: 2, L0805: 2, L0766: 2, S0126: 2, L0756: 2, L0755: 2, L0756: 2, L0755: 2, L0758: 2, H0170: 1, S0340: 1, S0010: 1, S0346: 1, L0471: 1, H0014: 1, H0373: 1, H0266: 1, S0334: 1, H0328:	S0338: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 2, L0784: 2, L0809: 2, L0665: 2, S0126: 2, L0740: 2, L0756: 2, L0755: 2, L0758: 2, H0170: 1, S0418: 1, S0360: 1, H0632: 1, H0036: 1, S0010: 1, S0346: 1, L0471: 1, H0014: 1, H0373: 1, H0266: 1, S0334: 1, H0328: 1, H0316: 1, S0036: 1,	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 2, L0784: 2, L0809: 2, L0766: 2, S0126: 2, L0740: 2, L0756: 2, L0758: 2, H0175: 2, L0758: 2, H0176: 1, H0632: 1, H0036: 1, 1, H0632: 1, H0036: 1, 1, H0014: 1, H0373: 1, H0266: 1, S0344: 1, H0328: 1, H0316: 1, S0366: 1, H0412: 1, H0202: 1, S0440:	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 2, L0784: 2, L0809: 2, L0665: 2, S0126: 2, L0740: 2, L0756: 2, L0755: 2, L0736: 2, L0755: 2, L0736: 1, H0632: 1, H0036: 1, H0632: 1, H0036: 1, H0266: 1, S0348: 1, H0373: 1, H0266: 1, S0348: 1, H0373: 1, H0266: 1, S0334: 1, H0328: 1, H0316: 1, S0336: 1, H0412: 1, H0202: 1, S0440:	10779: 6, L0777: 8, L0779: 6, L0766: 5, L0779: 6, L0362: 6, L0766: 5, L0752: 3, L0753: 3, L0779: 4, L0803: 3, L0759: 3, L0779: 4, L0803: 3, L0759: 3, L0784: 2, L0809: 2, L0372: 2, L0784: 2, L0809: 2, L0372: 2, L0756: 2, L0756: 2, L0756: 2, L0756: 2, L0756: 2, L0756: 3, L0756: 1, L0757: 1, H0014: 1, H0016: 1, S0036: 1, H0016: 1, S0036: 1, H0016: 1, S0036: 1, L0017: 1, H0016: 1, S0036: 1, L0018: 1, H0016: 1, S0036: 1, L0018: 1, H0016: 1, H0016: 1, S0036: 1, L0016: 1, H0016: 1, L0018: 1, L0016:	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 3, L0759: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0372: 1, L0784: 2, L0803: 2, L0665: 2, S0126: 2, L0768: 2, H0170: 1, S0418: 1, S0360: 1, H0632: 1, H0036: 1, S0010: 1, S0346: 1, L0471: 1, H0041: 1, H0373: 1, H0412: 1, H0202: 1, S0440: 1, S0150: 1, H0266: 1, S0422: 1, L0763: 1, L0638: 1, L0764: 1, L0773: 1,	S0358.8 L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0775: 4, L0803: 1, L0753: 3, H0171: 2, H0657: 2, S0222: 2, H0441: 2, L0805: 2, L0766: 2, S0126: 2, L0756: 2, L0756: 2, L0756: 2, H0170: 1, S0418: 1, S0360: 1, H063: 1, H0646: 1, S0400: 1, H0646: 1, H0412: 1, H0373: 1, H0412: 1, H0373: 1, H0412: 1, H0646: 1, S0422: 1, L0763: 1, L0638: 1, L0764: 1, L0773: 1, L0764: 1, L0773: 1, L07662: 1, L0764: 1, L0773: 1,	S0358: 8, L0777: 8, L0779: 6, L0362: 6, L0766: 5, L0752: 5, L0772: 4, L0803: 3, L0772: 3, H0717: 2, H0647: 2, L0372: 2, L0784: 2, L0809: 2, L0665: 2, S0126: 2, L0740: 2, L0756: 2, L0755: 2, L0756: 2, L0755: 2, L0756: 1, H0632: 1, H0635: 1, H0014: 1, H0373: 1, H0016: 1, S0346: 1, L0471: 1, H0316: 1, S0346: 1, H0016: 1, L0773: 1, H0016: 1, L0773: 1, L0662: 1, L0649: 1, L0804: 1, L0774: 1, L0666: 1,	10779: 6, L0362: 6, L0766: 5, L079: 6, L0362: 6, L0766: 5, L079: 5, L0759: 3, H0711: 2, H0657: 2, 2022: 2, H0441: 2, L0372: 2, L0784: 2, L0809: 2, L0760: 2, L0784: 2, L0809: 2, L0768: 2, L0785: 2, L0796: 1, L0786: 2, L0796: 1, L0786: 2, L0796: 1, H0036: 1, H0036: 1, S03010: 1, S0304: 1, H0037: 1, H0044: 1, H0037: 1, H0044: 1, L0764: 1, L0764: 1, L066: 1, L0764: 1, L0804: 1, L0764: 1, L0764: 1, L0804: 1, L0764: 1, L0691: 1, H0047:	\$ \$0358.8 \text{ L0779: 6, L0766: } \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	S0358: 8, 10777: 8, 10752: 6, 10766: 5, 10775: 4, 10752: 6, 10775: 4, 10775: 4, 10775: 4, 10775: 4, 10775: 4, 10775: 4, 10775: 4, 10775: 2, 10775: 2, 10776: 2, 10776: 2, 10776: 2, 10776: 2, 10776: 2, 10776: 2, 10776: 2, 10776: 2, 10776: 1, 10776: 1, 10776: 1, 10776: 1, 10777:	\$10738; 8, L0777; 8, L0778; 4, L0766; 5, L0766; 5, L0766; 5, L0766; 5, L0767; 4, L0803; 3, L0759; 3, H0171; 4, L0803; 3, L0759; 3, H0171; 2, L0872; 2, L07784; 2, L0784; 2, L0784; 2, L0784; 2, L0784; 2, L0786; 2, L0778; 3, H0170; 1, S0418; 2, L0778; 3, L0778; 3, L0784; 1, L0778; 4, H0328; 1, H0310; 1, S046; 1, L0471; 1, H0310; 1, S0046; 1, L0471; 1, L0774; 1, L0666; 1, L0774; 1, L0666; 1, L0774; 1, L0669; 1, L0774; 1, L0669; 1, L0774; 1, L0669; 1, H0319; 1, H0699; 1, H0319; 1, H0699; 1, H0649; 1, L0774; 1, L0666; 1, L0774; 1, L0666; 1, L0774; 1, L0666; 1, L0774; 1, L0666; 1, L0774; 1, L0669; 1, L0774; 1, L0669; 1, H0699; 1, H0669; 1, S0406; 1, S0406	\$\sqrt{6138i} \text{ \$1,0772i} \text{ \$2,022i} \text{ \$1,0772i} \text{ \$2,022i} \text{ \$1,0772i} \text{ \$2,0020i} \text{ \$2,0020i} \text{ \$2,0020i} \text{ \$1,0770i} \text{ \$2,0076i} \text{ \$2,0076i} \text{ \$2,0076i} \text{ \$2,0076i} \text{ \$1,0776i} \text{ \$2,0076i} \text{ \$1,0776i} \text{ \$1,077i} \t

		80-96, 33-	49								•													12-34, 98-	114
			-										<u>-</u>												
L0757: 1, H0445: 1, H0343: 1, S0011: 1, S0026: 1 and	H0543: 1.	i .		ARIU4: 2, ARU33: 2,		L0439: 6, L0731: 5, L0779:	4, H0622: 2, S0422: 2,	L0740: 2, L0756: 2, L0595:	2, H0402: 1, S0420: 1,	S0444: 1, H0580: 1, H0208:	1, L0717: 1, S0278: 1,	H0261: 1, S0222: 1, H0497:	1, H0574: 1, L0471: 1,	H0553: 1, H0641: 1, L0646:	1, L0764: 1, L0773: 1,	L0803: 1, L0804: 1, L0526:	1, L0791: 1, L0664: 1,	L0665: 1, H0520: 1, H0521:	1, H0522: 1, H0696: 1,	H0436: 1, L0777: 1, L0755:	1, L0759: 1, H0595: 1,	L0604: 1, H0543: 1 and	H0422: 1.	AR052: 2, AR053: 2,	AR039: 1, AR055: 1,
		Met-1 to Lys-6,	Glu-52 to Thr-58,	HIS-/2 to Ala-//.																					
		1532																						1533	
		154 -	471																					350-	694
		127								,														128	
		699216																						702658	
		HDABD32												-				vii La						HWACC64 702658	
		117												_										118	

				<u>e:</u>		.99		5:		<u></u>		ö		.8		·%		‡1:		35:		<u></u>		72:		.; 		.;.	
1, AR033: 1,	1, AR061: 1,	AR096: 0, AR104: 0	H0423: 10, H0445: 7,	H0556: 6, S0134: 5, H0656:	5, H0486: 5, H0657: 4,	4, H0134: 4, H04.	4, H0542: 4, H0543: 4,	H0422: 4, S0218: 3, H0125:	3; 3, H0581: 3,	3, L0761: 3, L076	3, H0710: 3, H0518: 3,	H0265: 2, S0114: 2, S0360:	2, H0580: 2, H0250: 2,	H0069: 2, H0004: 2, H0318:	2, S0142: 2, L0766: 2,	2, H0576: 2, L074	2: 1, H0221: 1,	H0220: 1, H0140: 1, H0341:	5: 1, H0589: 1,	H0638: 1, H0608: 1, H0635:	7: 1, S0474: 1,	H0050: 1, S0214: 1, H0428:	9: 1, H0634: 1,	H0063: 1, H0087: 1, H0272:	l: 1, S0450: 1,	S0144: 1, S0344: 1, L0762:	l, L0770: 1, L0769: 1,	L0667: 1, L0800: 1, L0774:	l, L0806: 1, L0776: 1,
AR060:	AR089:	AR096:	H0423:	H0556: (5, H0480	H0271:	4, H054	H0422:	3, S0278	H0090:	3, H0710	H0265:	2, H0580	H0069:	2, S0142	L0775: 2	2, T0002	H0220:	1, H025	H0638:	1, H042	H0050:	1, H003	H0063:	1, T0041	S0144: 1	1, L0770	T0967: 1	1, L0806
						0-11											-												

-	
.2: .2: .7:	70: 10: 11: 11:
L0655: 1, L0607: 1, L0661: 1, L0659: 1, L0809: 1, L0787: 1, L0664: 1, S0052: 1, S0053: 1, H0698: 1, H0701: 1, S0330: 1, S0378: 1, H0521: 1, H0214: 1, L0756: 1, L0779: 1, L0777: 1, L0755: 1 and H0136: 1.	AR055: 10, AR052: 9, AR053: 7, AR060: 6, AR061: 5, AR033: 5, AR096: 5, AR104: 5, AR089: 4, AR039: 3 L0776: 13, L0749: 8, L0776: 6, L0803: 5, L0770: 4, L0805: 4, H0100: 3, L0777: 3, L0789: 3, L0748: 3, L0745: 3, L0779: 3, L0777: 3, T0002: 2, H0090: 2, L0800: 2, L0809: 2, H0134: 2, L0756: 2, L0752: 2, L0758: 2, L0605: 2, H0170: 1, H0556: 1, H0341: 1, H0192: 1, S0476: 1, H0549: 1, S0222: 1, H0587: 1, H0013: 1, H0575: 1, T0103: 1, H0046: 1, H0067: 1, H0266: 1, H0284: 1, T0042: 1, L0796: 1, L0761:
L0655 1, L06 1, L0787 1, S00 H0701 1, H05 L0756 1, L07	
	Glu-49 to Gln-55, Asn-115 to Gln-136, Glu-154 to Asn-169, Ser-183 to Asn-191.
	1534
	534 -
	129
	703503
	HMWIW4 6
	119

	108-124	
	·	
	.235 .235 .23 .23	
03: 1, S012 0404: 1, 54: 1, L074 0755: 1, 59: 1, S002	23, AR055: 16, 14, AR096: 10, 9, AR060: 8, 7, AR033: 6, 4, AR104: 4, AR104: 5, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	0649:1,
L0636: 1, H0703: 1, S0126: 1, H0682: 1, S0404: 1, S0028: 1, L0754: 1, L0747: 1, L0750: 1, L0755: 1, L0757: 1, L0759: 1, S0026: 1 and H0136: 1.	AR052: 23, AR055: 16, AR053: 14, AR096: 10, AR089: 9, AR060: 8, AR061: 7, AR033: 6, AR039: 4, AR104: 4 L0747: 5, L0749: 5, L0764: 3, L0804: 3, L0755: 3, S0360: 2, H0135: 2, H0529: 2, H0696: 2, H0134: 2, S0406: 2, L0777: 2, L0731: 2, L0758: 2, L0362: 2, H0265: 1, H0294: 1, S0116: 1, S0418: 1, S0420: 1, S0132: 1, H0586: 1, H0333: 1, H0486: 1, H0156: 1, H0597: 1, H0178: 1, L0471: 1, H0617: 1, L0055: 1, H0594: 1, S0022: 1, H0551: 1, H0617: 1, L0055: 1, H0560: 1, S0448: 1, S0440: 1, H0646: 1, L0662:	1, L0766: 1, L0649:
L0 1,1 S00 11,1 L0	S, H G, H	<u>, </u>
,		
	1535	
	646	
	130	
	705030	
	HSDIJ72	
	120	

	80-99	42-59, 15-
L0783: 1, L0383: 1, L0382: 1, L0789: 1, L0666: 1, L0663: 1, H0520: 1, S0126: 1, H0689: 1, S0390: 1, L0751: 1, L0752: 1, L0759: 1, S0031: 1, S0260: 1, S0434: 1, L0597: 1, H0667: 1 and S0424: 1.	AR061: 165, AR033: 29, AR089: 28, AR060: 27, AR052: 5, AR055: 5, AR053: 5, AR096: 5, AR104: 2, AR039: 1 S0222: 2, L0439: 2, S0028: 1 and L0731: 1.	AR096: 6, AR053: 5, AR052: 5, AR055: 5, AR033: 4, AR060: 3, AR061: 3, AR089: 3, AR104: 2, AR039: 2 L0766: 7, H0521: 3, L0779: 3, H0543: 3, H0580: 2, H0509: 2, L0662: 2, L0803: 2, L0805: 2, H0519: 2, H0539: 2, L0756: 2, L0759: 2, H0542: 2, S0116: 1, S0354: 1, H0637: 1, H0574: 1, H0421: 1, S6028: 1, S0003: 1, S0214: 1,
	Met-1 to Leu-6, Ala-10 to Tyr-15, Arg-65 to Gln-70, Pro-107 to Glu-116.	
	1536	1537
	46 - 408	214 - 519
	131	132
	786907	707266
	HSLG034	HTOJF39
	121	122

HOG68: 1, HOS91: 1, HOS64: 1, SO210: 1, HOS29: 1, LOG64: 1, SO274: 1, HOG94: 1, HOG94: 1, HOG96: 1, HO			-	
HOORS: 1, HOS91: 1, HO264: 1, S0210: 1, HO329: 1, LO794: 1, L0604: 1, L0604: 1, S0374: 1, H0672: 1, LO774: 1, H0672: 1, LO774: 1, H0672: 1, LO774: 1, H0672: 1, LO774: 1, H0672: 1, Arg-66 to Tyr-74, AR039: 13, AR039: 14, Arg-66 to Tyr-74, AR039: 14, AR039: 5, HFIAW95 707878 134 129- 1539 Arg-39 to Thr-46, AR039: 14, AR099: 14, HFIAW95 707878 135 132- 1539 Arg-39 to Thr-46, AR039: 14, AR099: 14, AR061: 8, AR039: 14, AR062: 10, AR069: 14, AR063: 1, AR099: 17, AR069: 13, AR099: 17, AR069: 13, AR099: 17, AR069: 13, AR099: 17, AR069: 13, AR099: 11, AR069: 13, AR099: 11, AR069: 13, AR099: 11, AR069: 13, AR099: 13, AR069: 13, AR099: 13, AR069: 14, AR039: 14, AR069: 13, AR099: 13, AR069: 13, AR099: 13, AR069: 14, AR093: 14, AR093: 14, AR093: 11, AR093: 11, AR093: 11, AR093: 13, AR099: 13, AR093: 14, AR093: 13, AR099: 13, AR093: 14, AR093: 14, AR093: 11, AR093: 11,		45-62	77-95, 5- 21	51-68
HFIAW95 707378 135 - 362 1538 Ser-21 to Gly-28, AR053: 18, AR052: 17, Gly-36 to Arg-41, AR055: 15, AR096: 14, Arg-66 to Tyr-74, AR055: 15, AR096: 14, Arg-66 to Tyr-74, AR089: 11, AR060: 9, AR054: 1, 10436: 1 and S0194: 1. HFIAW95 707878 134 129- 1539 Arg-39 to Thr-46. AR039: 4, AR039: 18, AR033: 18, AR039: 14, AR065: 10, AR069: 14, AR089:				116806, 120120, 120120, 120120, 120436, 120436, 120436,
HFIAW95 707378 135 - 362 1538 Ser-21 to Gly-28, AR053: 18, AR052: 17, Gly-36 to Arg-41, AR055: 15, AR096: 14, Arg-66 to Tyr-74, AR055: 15, AR096: 14, Arg-66 to Tyr-74, AR089: 11, AR060: 9, AR054: 1, 10436: 1 and S0194: 1. HFIAW95 707878 134 129- 1539 Arg-39 to Thr-46. AR039: 4, AR039: 18, AR033: 18, AR039: 14, AR065: 10, AR069: 14, AR089:				3p21.3
HFIAW95 707398 133 36 - 362 1538 Ser-21 to Gly-28, Gly-36 to Arg-41, Arg-66 to Tyr-74. HFIAW95 707878 134 129 - 1539 Arg-39 to Thr-46. 533 HMEIU36 708053 135 132 - 1540 Ser-108 to Gln-125, G35	H0688: 1, H0591: 1, H0264: 1, S0210: 1, H0529: 1, L0794: 1, L0804: 1, L0664: 1, S0374: 1, H0672: 1, L0754: 1, H0445: 1, L0604: 1 and S0194: 1.	AR053: 18, AR052: 17, AR055: 15, AR096: 14, AR089: 11, AR060: 9, AR061: 8, AR033: 8, AR104: 7, AR039: 5 H0457: 2, T0023: 1, H0144: 1, H0436: 1 and H0677: 1.	47, AR033: 16, AR104: 14, AR096: 11, AR052: 10, AR061: 4, L0731: 2, 2, H0038: 1 ar	
HFIAW95 707878 134 129-533 HMEIU36 708053 135 132-635			Arg-39 to Thr-46.	
HFIA W95 707398 133 HFIA W95 707878 134 HMETU36 708053 135		1538	1539	
HFIA W95 707878 HFIA W95 707878 HMEIU36 708053		36 - 362	129 - 533	132 - 635
HFIA W95 HMEIU36		133	134	135
		707398	707878	708053
123		HPDEF35	HFIAW95	HMEIU36
		123	124	125

																								_					
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138320,	168468,	182280,	600163																										
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L0754: 9, S0422: 7, S0360:	6, L0794: 6, L0809: 6,	L0758: 6, H0265: 5, L0770:	5, L0805: 5, L0666: 5,	L0749: 5, L0755: 5, L0731:	5, S0414: 4, H0581: 4,	H0271: 4, L0771: 4, L0439:	4, L0591: 4, H0327: 3,	57: 3, H0266: 3, L080	3, L0776: 3, L0659: 3,	.0518: 3, L0665: 3, L0751:	3, S0434: 3, S0436: 3,	S0412: 3, H0656: 2, S0116:	2, S0212: 2, H0661: 2,	S0358: 2, S0132: 2, H0574:	2, H0156: 2, S0010: 2,	H0009: 2, H0123: 2, H0087:	2, H0551: 2, L0598: 2,	.0763: 2, L0761: 2, L0662:	2, L0766: 2, L0655: 2,	.0636: 2, L0664: 2, S0374:	2, H0547: 2, H0660: 2,	S0378: 2, H0436: 2, L0750:	2, L0756: 2, L0596: 2,	.0603: 2, H0136: 2, H0624:	1, H0556: 1, S0040: 1,	H0295: 1, S0114: 1, S0356:	1, S0442: 1, S0376: 1,	S0444: 1, H0730: 1, H0208:	, S0045: 1, S0476: 1,
T075	6, LO	1075	5, L0	L074	5, S0	H027	4, L0	H045	3, 10	L051	3, S0	S041	2, S0	8035	2, HC)00H	2, HC)T01	2, L0	1063	2, HC	S037	2, L0	0907	1, HC	H029	1, S0	S044	1, S0
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1, S0222:	5: 1,	1, H0486:	9: 1,	1, L0021:	5: 1,	l, H0318:): 1,	1, H0051:	I: 1,	, S0003:	l: 1,	1, H0038:	5: 1,	1, H0100:	1: 1,	, H0529:	: 1,	, L0764:	: 1,	, L0657:	: 1,	, L0663:	⊧ 1,	I, H0435:		, S0380:	1: 1,	1, S0044:	:1,
H0393: 1, H0351: 1, S0222:	: 1, H058	H0333: 1, H0642: 1, H0486:	1, H006	H0635: 1, H0427: 1, L0021:	1, H057	F0082: 1, H0253: 1, H0318:	: 1, L004	H0545: 1, H0024: 1, H0051:	: 1, H006	S0316: 1, H0687: 1, S0003:	l, H0688: 1, H0031: 1,	H0644: 1, H0617: 1, H0038:	: 1, H061	H0264: 1, H0059: 1, H0100:	, H0494: 1, H0561: 1,	, S0426: 1	1, L0638: 1, L0637: 1,	, L0800: 1	: 1, L0806	, L0527: 1	: 1, L5622	, L0791: 1	: 1, H014	, H0519:	1, H0658: 1, S0328: 1,	, H0539: 1	1, H0710: 1, H0521: 1,	H0522: 1, H0696: 1, S0044:	, S0027: 1, S0028: 1
H0393: 1	1, H0431	H0333: 1	1, H0013	H0635: 1	1, H0042	T0082: 1	1, H0251	H0545: 1	1, H0083	S0316: 1	1, H0688	H0644: 1	1, H0040	H0264: 1	1, H0494	S0440: 1	1, L0638	L0373: 1, L0800: 1, L0764:	1, L0626	L0653: 1	1, L0515	L0789: 1	1, S0053	L0565: 1	1, H0658	S0330: 1	1, H0710	H0522: 1	1, S0027
												-		7															
										_																		•	
							-															_							
													_															<u></u>	
							-																						

	192-213, 174-190	70-87
		120220, 120240, 123580, 151385, 171860, 190685, 236100,
		21922.3
L0742: 1, L0744: 1, L0745: 1, L0747: 1, L0752: 1, L0757: 1, L0759: 1, L0605: 1, L0595: 1, R0542: 1, H0543: 1, H0422: 1, H0423: 1, H0422: 1, S0042: 1, S0462: 1 and H0008: 1.	AR053: 3, AR096: 3, AR039: 2, AR052: 2, AR104: 2, AR033: 2, AR089: 2, AR060: 1, AR055: 1, AR061: 1 L0779: 5, L0157: 2, L0803: 2, L0754: 2, L0595: 2, H0305: 1, H0589: 1, H0638: 1, H0351: 1, H0486: 1, L0021: 1, H0318: 1, H0596: 1, S0150: 1, S0144: 11, L0364: 1, L0766: 1, L0809: 1, L0532: 1, H0667: 1 and H0542: 1.	AR033: 13, AR089: 12, AR060: 8, AR053: 8, AR039: 7, AR055: 6, AR052: 6, AR096: 5, AR061: 4, AR104: 3 H0038: 4, H0529: 3, L0803: 3, L0747: 3, L0779:
	Ser-76 to Ser-82.	Ala-16 to Glu-36, Arg-51 to Thr-56, Glu-104 to Thr-112.
	30 - 668 1541	95 - 748 1542
	136	137 95
ŀ		50 709347
	ННЕБМ89	127 HKABW60 709347
	126	127

	24.45, 97- 116, 67-84
236200, 240300, 267750, 600065, 601145	
3, H0341: 2, L0761: 2, L0794: 2, L0766: 2, L0805: 2, L0664: 2, L0777: 2, L0591: 2, L0485: 2, H0556: 1, H0583: 1, H0661: 1, H0662: 1, S0420: 1, S0410: 1, H033: 1, H0574: 1, S0280: 1, H0318: 1, H0014: 1, H0687: 1, S0003: 1, H0615: 1, L0055: 1, H0598: 1, L0451: 1, L0494: 1, S0344: 1, L0451: 1, L0369: 1, L0770: 1, L0769: 1, L0646: 1, L0773: 1, L0662: 1, L0773: 1, L0662: 1, L0773: 1, L0662: 1, L0773: 1, L0527: 1, L0438: 1, L0352: 1, S0390: 1, L0740: 1, L0750: 1, L0731: 1, L0757: 1, H0445: 1, L0592: 1 and H0543: 1.	AR096: 5, AR053: 3, AR061: 3, AR052: 3, AR033: 3, AR1089: 3, AR039: 3, AR104: 2, AR055: 2, AR060: 2 L0751: 6, H0510: 3, L0659: 3, L0439: 3, H0265:
3, H034. 1, 10591: 2 1, H058: 1 1, H066: 1 1, H068: 1 1, H0615: 1 1, L045: 1 1, L077: 1 1, L077: 1 1, L077: 1 1, L077: 1 1, L048: 1	AR096: AR061: AR033: AR039: AR055: L0751: L0659:
	1543
	79 - 627
	138
	710542
	HWLFB40
	128

	56-74, 38- 54, 89-105
38: 22: 50: 10: 17: 17:	
2, S0212: 2, S0418: 2, H0509: 2, L0773: 2, L0438: 2, L0748: 2, L0754: 2, L0731: 2, L0581: 2, H0556: 1, H0650: 1, L0005: 1, S6014: 1, H0581: 1, H0251: 1, H0178: 1, H0050: 1, L0471: 1, T0010: 1, H0673: 1, H0135: 1, H0673: 1, H0135: 1, L0770: 1, L0771: 1, L0768: 1, L0770: 1, L0771: 1, L0768: 1, L0770: 1, L0771: 1, L0666: 1, L0774: 1, L0776: 1, L0774: 1, L0776: 1, L0774: 1, L0777: 1, L07	AR039: 16, AR096: 11, AR053: 10, AR033: 9, AR052: 7, AR104: 7, AR089: 7, AR055: 6, AR060: 6, AR061: 3 L0438: 3, S0114: 1, H0580: 1, H0486: 1, H0706: 1, L0455: 1, H0561: 1, H0529: 1, H0658: 1 and L0439: 1.
	4 Lys-18 to Ser-24.
	139 54-410 154
	HDTDW40 710974
•	129 HI

122-138,	145-161										,	85-117								93-110							52-68, 94-
AR052: 45,	4R055: 24.	AR089: 23,	AR061: 11	0438: 2,	S0028: 2, H0656: 1, H0645:	S0222: 1,	S0346: 1, H0328: 1, H0029:	H0169: 1,	H0591: 1, H0646: 1, H0520:	L0746: 1 and		3, AR052: 2,	2, AR055: 2,	R089: 2,	2, AR061: 1,	1, AR104: 1	0752: 5,	H0553: 2, L0754: 2, L0749:	1.	8, AR033: 8,	.R096: 2,	2, AR053: 1,	1, AR039: 0,		0083: 1 and		AR053: 12,
AR039: 46, AR052: 45,	AR033: 27, AR055: 24.	AR104: 24, A	AR060: 18, A	L0439: 3, L0438: 2	S0028: 2, H06	1, H0369: 1, S0222: 1,	S0346: 1, H03	1, H0644: 1, H0169: 1,	H0591: 1, H0	1, H0539: 1, L0746: 1 and	L0366: 1.	AR096: 3, A	AR039: 2, A	AR033: 2, A	AR060: 2, A	AR053: 1, A	L0748: 6, L0752: 5	H0553: 2, LO	1 and L0780: 1.	AR089: 8, A	AR060:	AR061:	AR052:	AR104:	S0388: 1, H0083: 1 and	L0777: 1.	AR052: 17, AR053: 12,
																				Pro-8 to Thr-16,	Glu-50 to Glu-60,	Gln-67 to Arg-72,	Lys-81 to Asn-94.	•			1548 Met-1 to Arg-6,
1545												1546								1547							1548
7 - 825					_							275 -	90/							40 - 369							211 -
140												141								142							143
711111												711706								712570							714693
130 HEAAK34 711111												HLWAH41								HHSFI89							HSAVI33
130												131								132							133

WO 01/50304	
110	61-79, 78- 94
	22q13.33
AR033: 11, AR089: 8, AR060: 8, AR096: 7, AR061: 7, AR055: 4, AR104: 1, AR039: 0 L0740: 5, L0731: 5, L0439: 4, H0556: 3, L0766: 3, L0779: 3, H0657: 2, H0013: 2, H0578: 2, L0771: 2, L0748: 2, L0776: 2, L0748: 2, L0756: 2, L0777: 2, L0753: 2, L0601: 2, H0265: 1, S0114: 1, H0656: 1, H0580: 1, H0438: 1, H0333: 1, H0485: 1, H0486: 1, S0010: 1, H0052: 1, T0115: 1, S6028: 1, H0266: 1, L0674: 1, H0591: 1, S0002: 1, L0650: 1, L0515: 1, L0659: 1, L0556: 1, L0666: 1, L0663: 1, H0436: 1, L0749: 1, L0750: 1, L0758: 1, L0596: 1, H0668: 1, H0543: 1, H0423: 1 and H0472: 1	AR052: 5, AR096: 5, AR089: 4, AR033: 3, AR053: 3, AR055: 2, AR104: 2, AR060: 2,
Glu-31 to Arg-36, His-85 to Gly-92.	
·	1549
540	662 -
,	44
·	715359
	HMJAX17
	134

	171-188	48-64	111-127
AR039: 2, AR061: 2 L0439: 4, L0777: 3, H0658: 2, S0114: 1, S0360: 1, L0717: 1, H0391: 1, H0486: 1, L0157: 1, H0172: 1, H0083: 1, H0551: 1, H0517: 1, L0769: 1, L0521: 1, L0768: 1, L0805: 1, L0664: 1, H0521: 1 and H0555: 1.	AR096: 2, AR060: 1, AR053: 1, AR033: 1, AR089: 0, AR061: 0, AR055: 0, AR104: 0, AR052: 0	AR039: 76, AR052: 40, AR033: 39, AR096: 39, AR055: 38, AR104: 33, AR053: 33, AR089: 28, AR060: 24, AR061: 20 L0485: 2, S0282: 1, S0418: 1, H0002: 1, H0253: 1, H0196: 1, L0794: 1 and L0787: 1.	AR096: 1, AR052: 1, AR089: 1, AR060: 0, AR061: 0, AR033: 0, AR039: 0, AR053: 0
·		Ile-95 to Ala-101, Leu-110 to Ser-128.	Glu-22 to Ala-29, Ser-47 to Arg-58, Ser-108 to Tyr-113.
,	1550	1551	1552
	271 - 849	40 - 480	281 -
	145	146	147
	717449	718574	718768
	HLJDZ45	нанвс <i>57</i>	HLYDR60
	135	136	137

	94-110	76-99
S0182: 3, S0222: 2, H0445: 2, H0341: 1, H0151: 1, H0550: 1, T0039: 1, H0156: 1, H0275: 1, S0318: 1, S0316: 1, T0006: 1, H0040: 1, L0475: 1, S0344: 1, L0768: 1, L0766: 1, H0435: 1, L0750: 1, L0757: 1 and S0260: 1.	4, AR039: 3, 2, AR089: 2, 2, AR052: 1, 1, AR104: 1, 0, AR055: 0 1, S0280: 1, and H0593: 1.	AR033: 4, AR089: 4, AR061: 2, AR060: 1, AR052: 1, AR104: 1, AR039: 0, AR055: 0, AR096: 0, AR053: 0 L0805: 3, L0439: 3, H0674: 2, L0518: 2, L0809: 2, L0789: 2, L0751: 2, L0758: 2, H0390: 1, H0544: 1, H0570: 1, S0051: 1, F0006: 1, L0769: 1, L0800: 1, L0794: 1, L0803: 1, L0661: 1, L0636: 1, L0529:
S0182: 3, S0222: 2, H0445: 2, H0341: 1, H0151: 1, H0550: 1, T0039: 1, H0156: 1, H0275: 1, S0318: 1, S0316: 1, T0006: 1, H0040: 1, L0475: 1, S0344: 1, L0768: 1, L0766: 1, H0435: 1, L0750: 1, L0757: 1 and S0260: 1.	AR033: 4, AR039: AR096: 2, AR089: AR061: 2, AR052: AR060: 1, AR104: AR053: 0, AR055: H0484: 1, S0280: 1, H0373: 1 and H0593:	AR033: 4, AR089: 4, AR061: 2, AR060: 1, AR052: 1, AR104: 1, AR039: 0, AR055: 0, AR096: 0, AR053: 0 L0805: 3, L0439: 3, H0674: 2, L0518: 2, L0809: 2, L0789: 2, L0751: 2, L0758: 2, H0390: 1, H0544: 1, H0570: 1, S0051: 1, T0006: 1, L0769: 1, L0800: 1, L0794: 1, L0803: 1, L0661: 1, L0636: 1, L0529:
		Arg-11 to Gly-16, Pro-35 to Phe-44.
	1553	1554
	10 - 372	105 - 431
	148	149
	719977	720237
	нснмоо	HADMD75
	138	139

	89-107
	·
1, S0406: 1, md	3, 1, 1, 1, 1, 1, 1, 80222: 2, 2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
, L0665: 10694: 1, , L0779: 0731: 1 a	3, AR096: 2, AR053: 1, AR104: 1, AR061: 10, L0803: 3, H0486: 3, H0486: 3, H0591: 2, H0561: 1, L0760: 1, H0675: 1, H0653: 1, H0659:
1, L0543: 1, L0665: 1, H0696: 1, H0694: 1, S0406: 1, L0747: 1, L0779: 1, L0777: 1, L0731: 1 and H0352: 1.	AR052: 3, AR096: 3, AR033: 2, AR053: 1, AR039: 1, AR104: 1, AR055: 1, AR104: 1, AR060: 1, AR061: 1 L0794: 10, L0803: 4, S0045: 3, H0486: 3, H0013: 3, H0251: 3, H0591: 3, H0265: 2, S0360: 2, S0222: 2, L0758: 2, L0591: 2, L0809: 2, H0519: 2, L0439: 1, R0114: 1, L0760: 1, H0255: 1, S0444: 1, H0432: 1, H0557: 1, H0632: 1, H0492: 1, H06575: 1, L0435: 1, H0494: 1, H0641: 1, L0688: 1, L0761: 1, L0766: 1, L0774: 1, L0653: 1, L0663: 1, H0144: 1, L0438: 1, H0689: 1, H0659: 1, H0689: 1, H0659: 1,
	HO, 10, 10, 10, 10, 10, 10, 10, 10, 10, 10
	Ala-7 to Lys-28, Gly-45 to Lys-55.
	1555
	51 - 473
	720269
	HKADW4
	140

0 01/90.	304																								/10	750
	62-78			-																						
																				•••						
1, L0754: 1, L0747: 1, L0750: 1, L0752: 1, S0434: 1, L0595: 1 and L0366: 1.	AR055: 16, AR039: 15,	AR052: 10, AR089: 10,	AR096: 10, AR104: 9,	AR060: 8, AR061: 7	L0769: 4, S0126: 4,	L0758: 4, L0755: 3, S0358:	2, S0444: 2, H0617: 2,	H0673: 2, L0764: 2, S0374:	2, L0748: 2, L0779: 2,	L0592: 2, H0716: 1, H0656:	1, H0341: 1, S0418: 1,	S0420: 1, H0675: 1, S0408:	1, H0580: 1, S0046: 1,	S0300: 1, H0632: 1, H0013:	1, S0280: 1, L0043: 1,	H0606: 1, H0316: 1, S0150:	1, S0344: 1, L0762: 1,	L0763: 1, L0761: 1, L0771:	1, L0766: 1, L0774: 1,	L0775: 1, L0375: 1, L0655:	1, L0382: 1, H0144: 1,	H0690: 1, S0328: 1, H0710:	1, H0521: 1, L0744: 1,	L0786: 1, L0731: 1, H0445:	1, H0667: 1, S0276: 1,	H0543: 1, H0422: 1 and
	Gly-10 to Glu-16,	GIII-00 10 LCu-39.																								
	1556																									
	28 - 327																									
	151	,								<u></u>																
-	721084																									-
	HFAUL30																					-				

	70-87	71-87
	420: 7773:	1, 4, 8, 6, 0754: 0551: 352:
	AR104: 10, AR033: 7, AR052: 6, AR089: 4, AR053: 4, AR096: 3, AR039: 3, AR060: 3, AR055: 2, AR061: 0 L0766: 4, H0494: 2, L0755: 2, S0040: 1, S0420: 1, S0046: 1, S0132: 1, S0222: 1, H0438: 1, H0250: 1, S0010: 1, H0038: 1, H0538: 1, L0800: 1, L0773: 1, H0670: 1 and L0777: 1.	AR053: 42, AR096: 31, AR052: 30, AR089: 24, AR033: 23, AR104: 18, AR039: 18, AR055: 16, AR060: 16, AR061: 8 L0439: 9, H0013: 3, H0090: 2, H0561: 2, L0754: 2, L0731: 2, H0170: 1, H0341: 1, H0580: 1, H0485: 1, L0471: 1, H0024: 1, H0644: 1, H0591: 1, H0551: 1, L0766: 1, L0606: 1, L0659: 1, L0438: 1, L0352: 1, H0672: 1, H0521: 1, H0436: 1, H0627: 1, L0748:
S0446: 1	AR104: AR052: AR039: AR039: AR039: L0766: L0755: 2 1, S0046: S0222: 1 1, S0010: H0538: 1 1, H0670	AR053: 42, AI AR052: 30, AI AR033: 23, AI AR039: 18, AI AR060: 16, AI L0439: 9, H05 2, L0731: 2, H05 1, L0471: 1, H05 1, L0766: 1, L0 L0659: 1, L043 1, H0672: 1, H06 H04436: 1, H06 1 and H0542: 1
		Leu-14 to Glu-23, Lys-41 to Arg-50, Pro-90 to Gln-96.
	1557	1558
	181 - 609	42 - 401
	152	153
	721126	721141
	HKADD23	HE8MO09
	142	143

106-127, 56-77, 80- 98	42-58, 73- 89, 120- 136	77-97, 14- 31
AR039: 20, AR089: 18, AR052: 18, AR053: 17, AR096: 17, AR033: 15, AR055: 15, AR104: 14, AR060: 13, AR061: 6 H0013: 1, L0761: 1 and L0779: 1.	AR089: 6, AR033: 5, AR060: 5, AR053: 3, AR096: 3, AR061: 2, AR052: 2, AR104: 1 H0617: 9, H0549: 4, S0406: 4, L0439: 3, H0717: 2, H0255: 2, S0358: 2, H0550: 2, S0049: 2, H0494: 2, L0777: 2, H0713: 1, H0716: 1, H0484: 1, S0356: 1, S0132: 1, H0619: 1, L0021: 1, H0421: 1, H0457: 1, S0366: 1, H0379: 1, S0344: 1, L0657: 1, L0639: 1, L0761: 1, L0803: 1, L0774: 1, L0657: 1, L0783: 1, L0789: 1, H0593: 1, H0539: 1, H0436: 1 and	AR055: 11, AR060: 7, AR096: 5, AR033: 5,
 	 	44
1559 Met-1 to Gly-7.	1560 Met-1 to Cys-18.	
1559	1560	1561
213 - 593	- 124 - 600	34 - 591
154	155	156
721418	722648	722943
144 HE8FL67	HEOOA49	HMSJH49
44	145	146

	1-25, 86- 119, 142- 159, 79-95	89-107, 6- 22	41-58
	102540, 103581, 118511, 146150, 227220, 243500, 261623, 601889, 601889,		
	15q13-q14		
AR052: 5, AR061: 5, AR039: 4, AR089: 3, AR053: 3, AR104: 3 L0539: 2, H0546: 1, S0386: 1, H0560: 1, S0002: 1, L0741: 1 and L0746: 1.	AR060: 9, AR104: 8, AR096: 8, AR055: 8, AR039: 7, AR089: 7, AR033: 7, AR052: 6, AR053: 5, AR061: 5 L0740: 20, L0745: 8, L0777: 5, T0082: 2, L0758: 2, H0251: 1 and L0747: 1.	AR096: 3, AR039: 1, AR052: 1, AR089: 1, AR060: 1, AR055: 0, AR061: 0, AR033: 0, AR053: 0, AR104: 0 H0341: 1 and H0486: 1.	AR061: 1, AR033: 1, AR039: 0, AR089: 0, AR053: 0, AR096: 0, AR055: 0, AR060: 0, AR052: 0, AR104: 0
	Pro-28 to Ser-33, Pro-66 to Arg-79, Ser-163 to Gly-180.		Met-1 to Ala-7, His-24 to Pro-35.
	1562	1563	1564
	218 - 910	48 - 395	318 -
	157	158	159
	723491	724196	724352
	HARAX45	HDTES50	НК GВС30
	147	148	149

_			
	90-106, 42-58	43-59	221-238, 54-70
		126650, 126650, 154276, 173360, 173360, 602136, 602136, 602136,	116806, 120120, 120120, 120436, 120436, 120436, 138320, 168468, 182280, 600163
		7422	3p21.3
	AR052: 19, AR055: 18, AR089: 17, AR053: 14, AR033: 11, AR061: 9, AR060: 9, AR096: 8, AR039: 0, AR104: 0 L0766: 4, H0441: 1, L0744: 1 and L0596: 1.	AR039: 53, AR055: 28, AR053: 27, AR033: 23, AR052: 21, AR096: 21, AR104: 21, AR089: 18, AR060: 15, AR061: 13 H0618: 8 and H0253: 4.	AR104: 4, AR033: 4, AR089: 3, AR053: 3, AR052: 3, AR096: 2, AR061: 2, AR060: 2, AR055: 2, AR039: 2 L0803: 6, L0771: 5, L0439: 5, L0769: 4, L0805: 4, L0759: 4, L0747: 3, L0777: 3, L0758: 3, H0156: 2, H0618: 2, H0052: 2, H0545: 2, L0163: 2, H0644: 2, S0440: 2, L0644: 2,
	Glu-10 to Asn-15, Val-73 to Arg-83, Gly-118 to Ser-128.	Met-1 to Ser-7.	Glu-122 to Lys-127, Glu-161 to Val-168, Thr-178 to Trp-189.
	1565	1566	1567
	90 - 500	218 - 577	127 - 888
	160	161	162
	724432	724950	725228
	HKIXO37	HTLF139	неовля1
	150	151	152

		22-63, 51- 67
565: 624: 6657: 0009: 1100: 126: 126: 751:	1.	0, %
L0766: 2, L0653: 2, L0665: 2, H0539: 2, L0748: 2, L0731: 2, L0593: 2, H0624: 1, H0556: 1, T0002: 1, H0713: 1, H0650: 1, H0657: 1, H0402: 1, S0132: 1, H0619: 1, L0717: 1, S0278: 1, H0642: 1, H0486: 1, H0642: 1, H0648: 1, H0649: 1, H0648: 1, H0649: 1, H0679: 1, H0649: 1, H0679: 1, H0647: 1, S0144: 1, H0529: 1, L0763: 1, L0662: 1, L0775: 1, L0776: 1, L0763: 1, L0663: 1, H0649: 1, H0666: 1, L0663: 1, H0649: 1, H0649: 1, L0750: 1, H0658: 1, L0776: 1, L0663: 1, H0649: 1, L0750: 1, H0678: 1, L0750:	1, H0423: 1 and H0677: 1	AR033: 28, AR060: 19, AR104: 19, AR089: 18,
L0766: 2, 2, H0539: L0731: 2, H0539: 2, H0539: 1, H0556: H0713: 1, 1, H0402: S0132: 1, 1, S0278: H0548: 1, 1, H0620: H0083: 1, 1, H0674: H0561: 1, H0561: 1, L0772: 1, 1, L0363: L0772: 1, 1, L0363: L0772: 1, 1, L0363: L0772: 1, 1, L0363: L0775: 1, 1, L0435: S0332: 1, L0750: 1,	1, H0423:	AR033: 2 AR104: 1
		1568 Met-1 to Lys-11, Gln-72 to Gly-77.
		1568
		215 - 568
		163
		725655
		HAGES18
		153

	69-85, 27- 44, 112- 128
	-
AR096: 13, AR061: 8, AR055: 6, AR053: 5, AR052: 5, AR039: 3	AR104: 21, AR033: 17, AR055: 11, AR060: 6, AR061: 6, AR039: 6, AR089: 6, AR053: 5, AR089: 6, AR053: 5, AR089: 4, AR096: 4 L0439: 13, H0052: 8, L0769: 5, L0755: 5, L0770: 4, L0754: 4, L0753: 4, L0758: 4, L0794: 3, L0775: 3, L0806: 3, L0776: 3, L0752: 3, S0360: 2, H0261: 2, S0388: 2, H0213: 2, L0804: 2, L0774: 2, L0807: 2, L0779: 2, L0603: 2, S0256: 1, H0255: 1, H0455: 1, H0009: 1, H0172: 1, S0364: 1, S0036: 1, H0038: 1, H0131: 1, L0764: 1, L0803: 1, L0805: 1, L0809: 1, L0787: 1, L0790: 1, L0663: 1, H0521: 1, L0742: 1, L0751: 1, L0745: 1, L0731: 1 and L0485: 1.
	Arg-14 to Pro-20.
	1569
	183 - 575
	164
	725822
	HHSGV20
	154

AR096: 4, AR055: 3, AR032: 2, AR060: 2, AR052: 2, AR089: 2, AR053: 2, AR061: 2, AR104: 0 L0731: 8, L0794: 7, L0803: 4, H0265: 3, L0809: 2, H0556: 1, S0134: 1, H0657: 1, H0341: 1, S0356: 1, H0411: 1, S0222: 1, H0657: 1, H0013: 1, H0618: 1, H0573: 1, L0667: 1, H0657: 1, L0668: 1, L0789: 1, L0668: 1, L079: 1, L0805: 1, L0636: 1, L079: 1, L0805: 1, L0636: 1, L079: 1, L0805: 1, L0608: 1 and L0777: 1, L0780: 1, L0758: 1, L0759: 1, L0608: 1 and L0361: 1. AR052: 4, AR039: 3, AR104: 3, AR033: 2, AR055: 2, AR060: 2, 180200, AR053: 2, AR055: 2, 180200, AR053: 2, AR055: 2, 180200,
4, AR055: 3, 3, AR060: 2, 2, AR089: 2, 2, AR061: 2, 0 8, L0794: 7, 4, H0265: 3, L0809: 5: 3, L0766: 2, 2, L0565: 2, L0595: 6: 1, S0134: 1, 1, H0341: 1, S0356: 1: 1, S0222: 1, 1, H0013: 1, H0618: 7: 1, H0050: 1, 1, L0670: 1, 1, L0644: 2: 1, L0804: 1, 1, L0636: 1, L0789: 3: 1, L0779: 1, 1, L0608: 1 and 4, AR039: 3, 3, AR039: 3, 13q14.1- 136533, 3, AR039: 2, 180200, 2, AR060: 2, 180200, 2, AR065: 2, 180200,
4, AR055: 3, 3, AR060: 2, 2, AR089: 2, 2, AR061: 2, 0 8, L0794: 7, 4, H0265: 3, L0809: 5: 3, L0766: 2, 2, L0565: 2, L0595: 6: 1, S0134: 1, 1, H0341: 1, S0356: 1: 1, S0222: 1, 1, H0013: 1, H0618: 7: 1, H0050: 1, 1, H0179: 1, H0292: 3: 1, L0804: 1, 1, S0422: 1, L0789: 3: 1, L0636: 1, L0789: 5: 1, L0704: 1, H0215: 5: 1, L0709: 1, 2, AR039: 3, 3, AR033: 2, 2, AR065: 2, 2, AR065: 2,
R096: 4, AR055: 3, R052: 2, AR060: 2, R053: 2, AR060: 2, R053: 2, AR061: 2, R104: 0 L0731: 8, L0794: 7, 0803: 4, H0265: 3, L0809: , L0596: 3, L0766: 2, 0659: 2, L0565: 2, L0595: , H0556: 1, S0134: 1, 0104: 1, H0013: 1, H0618: , H0557: 1, H0013: 1, H0618: , H057: 1, H0079: 1, 0620: 1, H0179: 1, H0292: , H0553: 1, L067: 1, 0805: 1, L0636: 1, L0789: , L0665: 1, S0126: 1, 0777: 1, L079: 1, H0215: , L0786: 1, L0779: 1, 0777: 1, L0780: 1, L0758: , L0786: 1, L0608: 1 and 0361: 1. R052: 4, AR039: 3, R104: 3, AR033: 2, R096: 2, AR060: 2, R096: 2, AR055: 2,
1570 Pro-13 to Ser-19, Ala-21 to Asp-30, Gln-41 to Val-48, Asp-108 to Leu-113.
1571
117 - 554 71 - 403
165
727386
155 HNECD53 727386 156 HRAAO53 728064
155

			304																								1 3 0.		
631																		•											
600631					_																				_				
20,	5,	. 4,	1,	.0,	oʻ		H0539:	, 6	H0457:	°,	H0519:	6,	S0003:	6,	L0756:	6,	S0356:	5,	L0655:	5,	L0362:	4,	S0408:	4,	H0031:	4,	T0041:	4,	L0653:
L0747: 21, L0740: 20,	, L0663: 1	L0748: 1	.0662: 12, L0665: 11,	, H0013: 1	H0672: 1	.0758: 10, H0486: 9	.0766: 9,	9, L0599:	30222: 8,	8, H0423:	L0471: 7,	7, H0657:	H0024: 6,	5, L0775:	L0744: 6,	5, S0434:	30116: 5,	5, H0014:	L0646: 5,	5, H0696:	.0608: 5,	5, S0134:	H0650: 4,	t, L0717:	H0622: 4,	4, H0591:	T0067: 4,	4, L0768:	.0375: 4,
L0747: 2	H0144: 17	L0666: 14, L0748: 14,	.0662: 12	H0656: 10, H0013: 10,	.0659: 10,	.0758: 10,	S0422: 9, L0766: 9, H0539:	9, L0731: 9, L0599: 9,	S0360: 8, S0222: 8, H0457:	8, H0090: 8, H0423: 8,	H0050: 7, L0471: 7, H0519:	7, H0648: 7, H0657: 6,	S0358: 6, H0024: 6, S0003:	6, L0598: 6, L0775: 6,	.0776: 6, L0744: 6, L0756:	5, L0777: 6, S0434: 6,	50026: 6, 50116: 5, 50356:	5, S0444:	L0637: 5, L0646: 5, L0655:	5, L0809: 5, H0696: 5,	S0436: 5, L0608: 5, L0362:	5, S0412: 5, S0134: 4,	H0583: 4, H0650: 4, S0408:	4, S0045: 4, L0717: 4,	H0046: 4, H0622: 4, H0031:	4, H0163: 4, H0591: 4,	H0040: 4, T0067: 4, T0041:	4, L0764: 4, L0768: 4,	L0774: 4, L0375: 4, L0653
		_=					<u> </u>	<u> </u>	<u> </u>	<u></u>			<u> </u>				<u> </u>	41	<u> </u>	<u>.y.,ı</u>	<u> </u>	<u>,4 1</u>							
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4, \$0374: 4, L0438: 4, H0520: 4, H0670: 4, H0555: 4, L0754: 4, L0750: 4, L0755: 4, L0757: 4, L0591: 4, L0361: 4, H0422: 4, H0624: 3, H0341: 3, \$0442:	3, S0376: 3, S0007: 3, H0441: 3, H0586: 3, H0036: 3, H0581: 3, H0052: 3, H0266: 3, H0553: 3, H0644: 3, H0038: 3, H0551: 3, H0647: 3, H0646: 3, L0771:	3, L0517; 3, L0664; 3, H0593; 3, H0660; 3, S0406; 3, L0745; 3, L0746; 3, L0752; 3, H0445; 3, S0192; 3, H0542; 3, H0170; 2, H0716; 2, H0662; 2, H0580; 2, H0619; 2, S0278; 2, H0369; 2, S0414; 2, T0060; 2, H0156; 2, H0599; 2, S0049; 2, H0178; 2, L0163; 2, H0051; 2, S0388; 2,	H0083: 2, H0252: 2, H0328: 2, H0615: 2, H0688: 2, T0023: 2, H0674: 2, L0455: 2, H0068: 2, H0135: 2, H0100: 2, S0440: 2, H0641: 2, S0002: 2, L0520: 2, L0641: 2, L0794: 2, L0651:

2, L0555: 2, L0526: 2, L0518: 2, L0545: 2, H0547:	2, H0684: 2, H0658: 2, S0328: 2, H0478: 2, S0028:	2, L0439; 2, L0751; 2,	2779: 2, S0031: 2, L0605:	2, L0590: 2, H0543: 2, S0452: 2, L0411: 1, H0171:	L0615: 1, H0265: 1,	0556: 1, H0686: 1, S0040:	l, S0342: 1, H0713: 1,	H0255: 1, H0661: 1, H0459:	H0638: 1, S0420: 1,	0329: 1, S0046: 1, S0132:	1, H0393: 1, S6026: 1,	H0549: 1, H0550: 1, H0461:	l, H0370: 1, H0600: 1,	0587: 1, H0333: 1, H0331:	1, H0574: 1, H0485: 1,)586: 1, H0069: 1, H0635:	1, T0082: 1, H0590: 1,	0010: 1, S0346: 1, H0318:	H0374: 1, H0194: 1,	0110: 1, L0738: 1, H0572:	1, H0123: 1, H0012: 1,	H0015: 1, H0373: 1, S0051:	H0356: 1, H0239: 1,	0594: 1, S6028: 1, H0267:	1, H0271: 1, H0188: 1,	H0428: 1, H0039: 1, L0194:
2, LC			<u></u>	 S.C.)H	1,	H	11,	<u>H</u>	11,)H	1,)H	11,	27	T,	OS	<u> </u>)HI		<u> </u>		HC
																						-				
											· · ·		··- <u>-</u>	-						_			· ·	_		

	40-72
1, H0667: 1, S0276: 1, S0424: 1, S0462: 1, S0456: 1, H0008: 1 and H0352: 1.	AR096: 1, AR104: 1, AR089: 1, AR060: 1, AR061: 0, AR033: 0, AR052: 0, AR052: 0, AR055: 0, AR052: 0, L0740: 10, H0521: 8, L0659: 7, L0666: 7, L0731: 7, L0664: 6, L0754: 6, L0803: 5, L0752: 5, S0003: 4, L0770: 4, L0771: 4, L0438: 4, H0547: 4, S0380: 4, S0152: 4, H0171: 3, S0212: 3, S0358: 3, H0623: 3, S0344: 3, R0520: 3, S0126: 3, H0545: 3, H0539: 3, L0602: 3, L0744: 3, L0750: 3, L0758: 3, L0599: 3, S0026: 3, S0192: 3, S0242: 3, L0483: 2, H0169: 2, H0590: 2, H0510: 2, H0375: 2, H0560: 2, L0775: 2, H0560: 2, L0777: 2, H0667:
	Tyr-5 to Gly-13, AR096: Ala-23 to Leu-38, AR089: Tyr-82 to Leu-95, AR061: Asn-126 to Asp-146, AR039: Pro-153 to Pro-167. AR055: L040: L040: L0438: 4, L077 L0438: 3, S0155: H0548: 3, H052: H0648: 3, L0748: L0483: C, H051: L0483: C, H051: L0483: C, H0560: C, L0766: C, H0560: C, L0766: C, H0560: C, L0766: C, H0560: C, L0766: C, L0766: C, L0766: C, H0560: C, L0766: C,
	1572
	863
	167
	728098
	HDPGD34
	157

422: 2, 5: 1, S0040:	.16: 1,	208: 1,	D: 1, H0574:	590: 1,	i: 1, S0474:	596: 1,	6: 1, L0471:	024: 1,	3: 1, S0388:	028: 1,	5: 1, H0428:	553: 1,	2: 1, H0598:	040: 1,	3: 1, H0551:	269: 1,	l: 1, L0065:	541: 1,	9: 1, L0763:	300: 1,	3: 1, L0804:	519: 1,	3: 1, L0665:	593: 1,	9: 1, H0670:	596: 1,	8: 1, H0134:
2, H0543: 2, H0422: 2, H0624: 1, H0265: 1, S0040:	1, S0134: 1, S0116: 1, S0418: 1 H0580	1, H0329: 1, H02	S0045: 1, H0370: 1, H0574:	1, T0040: 1, H0590: 1,	80010: 1, 80346:	1, H0263: 1, H0596: 1,	H0544: 1, H0546	1, T0003: 1, H0024: 1,	S0050: 1, H0373: 1, S0388:	1, H0083: 1, S60	S0214: 1, H0615	1, H0622: 1, H0553: 1,	L0142: 1, H0032: 1, H0598:	1, S0036: 1, H0040: 1,	H0616: 1, H0063	1, H0268: 1, H0269: 1,	S0386: 1, T0041	1, S0150: 1, H0641: 1,	H0529: 1, L0369	1, L0667: 1, L08	L0764: 1, L0648	1, L0651: 1, L05	L0788: 1, L0663	1, H0144: 1, H05	H0690: 1, H0659: 1, H0670:	1, S0330: 1, H0696: 1,	H0694: 1, S0168: 1, H0134:
	14.																										
													-														

	42-63, 12-28	230-267, 2-18, 87- 103	88-105, 60-76
1, H0555: 1, H0436: 1, H0478: 1, S0027: 1, S0028: 1, L0439: 1, L0688: 1, L0583: 1, L0362: 1, L0366: 1, H0668: 1, S0196: 1, H0542: 1, H0423: 1, S0456: 1 and S0021: 1.	AR096: 1, AR052: 1, AR104: 1, AR033: 1, AR089: 0, AR053: 0, AR055: 0, AR061: 0, AR060: 0 L0766: 5, L0748: 3, L0758: 3, L0791: 2, S0328: 2, L0747: 2, L0777: 2, H0251: 1, H0673: 1, L0803: 1, L0806: 1, L0665: 1, H0547: 1, H0436: 1, L0759: 1, H0445: 1 and L0759: 1, H0445: 1 and L0759: 1,	AR096: 2, AR055: 1, AR089: 1, AR033: 1, AR060: 1, AR061: 0, AR053: 0, AR039: 0, AR104: 0, AR052: 0 H0457: 1 and H0521: 1.	AR061: 0, AR060: 0, AR096: 0, AR033: 0,
. ,	Thr-35 to Lys-40, Pro-63 to Gin-69, Leu-122 to Thr-128.	Tyr-81 to Ile-88, Ala-113 to Gln-118, Asn-183 to Ser-189.	7
	1573	1574	1575
	212 - 769	157 - 972	95 - 445
	168	169	170
	728763	728861	728903
	HLYBU12	HEONV59	160 HCWHX54
	158	159	160

				103-119,	55-71												-				,						43-62, 1-	17
AR052: 0, AR039: 0,	AR104: 0, AR089: 0,	AR055: 0, AR053: 0	H0305: 1 and H0423: 1.	AR053: 19, AR052: 17,	AR089: 12, AR096: 12,	AR055: 12, AR060: 8,	AR033: 7, AR061: 5,	AR104: 4, AR039: 3	L0766: 4, L0779: 4,	L0803: 3, L0747: 3, L0752:	3, H0039: 2, H0059: 2,	L0794: 2, S0027: 2, L0744:	2, L0740: 2, L0777: 2,	L0759: 2, S0430: 1, S0418:	1, S0358: 1, S6014: 1,	H0497: 1, H0013: 1, H0575:	1, H0123: 1, H0510: 1,	H0040: 1, L0761: 1, L0662:	1, L0804: 1, L0774: 1,	L0775: 1, L0776: 1, L0384:	1, L0787: 1, L0663: 1,	H0702: 1, H0547: 1, H0682:	1, H0696: 1, L0749: 1,	L0753: 1, L0731: 1, H0445:	1, H0595: 1, S0276: 1 and	H0542: 1.	AR039: 53, AR033: 27,	AR096: 21, AR055: 20,
				Arg-26 to Gln-35,	Arg-41 to Asn-46,	Tyr-80 to Ser-85.											***										1577 Phe-22 to Asn-33,	Ala-68 to Gly-73.
				9251																							1577	
				739 -	1101																						113 -	439
				171																							172	
				730794																							730924	
				HE8DF23				_																			HOECO53	
				161													_										162	

•			
			
54:	60: 44: 43:	47: 341: 069 510 710:	45: 36:
18 18 15 15 15 16 17 19	3, 105	LOC HOO:	2, 207, 2, 2,
.4. 56.09 .4. 57. 4.	76: 4, 45: 33, 13, 13, 13, 13, 13, 13, 13, 13, 13,	6, 2, 2, 6, 2, 6, 2, 6, 7, 6, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7,	2, H0696: 2, S3014: 2, S0028: 2, L0742: 2, LC 2, L0750: 2, L0755: 2, L0757: 2, H0445: 2, S(2, H0542: 2, H0423: 2,
4R1 4RC 4RC 5076 500 500 617	758: 758: 7004: 778: 78: 78: 742: 96:	751: 104: 105: 105: 101: 101: 105: 106: 106: 106: 106: 106: 106: 106: 106	330 242 375 404 404
19,7 10,1 10,1 10,1 10,1 10,1	4, 1 LO7 1, S 3, S 3, I 3, I 3, I	3, 1 3, 1 40, 1 10, 1 10, 1 10, 1	2, S LO7 2, I HO 2, F
3: 1 2: 1 6: 1 6: 1 7: 4,			5,50,5
AR053: 19, AR104: 18, AR052: 18, AR089: 18, AR061: 15, AR060: 15 S0126: 10, L0766: 5, S0027: 5, L0748: 5, L0754: 5, H0484: 4, S0007: 4, H0370: 4, H0617: 4, H0087:	4, L0803: 4, L0776: 4, L0744: 4, L0758: 4, S0360: 3, S0408: 3, S0045: 3, S0046: 3, S0278: 3, H0544: 3, H0545: 3, H0023: 3, S0144: 3, S0142: 3, L0773: 3, L0794: 3, L0655: 3,	L0659: 3, L0751: 3, L0747: 3, H0543: 3, H0422: 3, S0040: 2, H0295: 2, H0341: 2, S0029: 2, H0549: 2, H0441: 2, H0486: 2, H0069: 2, H0530: 2, H0150: 2, H0050: 2, H0677: 2, H0510: 2, H0424: 2, H0634: 2, H0551: 2, L0763: 2, L0646: 2, L0378: 2, L0806: 2, L0805: 2, H0539: 2, H0710:	2, H0696: 2, S3014: 2, S0028: 2, L0742: 2, L0745: 2, L0750: 2, L0755: 2, L0757: 2, H0445: 2, S0436: 2, H0542: 2, H0423: 2,
ARARA SO S. 1	2, 12 2, 13 3, 13 3, 13 3, 13	1, H 2, H 3, S 3, J 1, S 1	2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
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H0170: 1, H0171: 1, H0556:	H0294: 1, S0114: 1, H0657:	1, H0656: 1, H0381: 1,	S0116: 1, S0282: 1, H0638:	, H0125: 1, S0442: 1,	H0728: 1, S0132: 1, S6022:	0222: 1, H0392: 1,	92: 1, S0280: 1, L0021:	0082: 1, H0618: 1,	S0049: 1, H0251: 1, H0309:	10327: 1, H0178: 1,	H0567: 1, H0081: 1, H0012:	1, 50054: 1, 50051: 1,	H0083: 1, H0594: 1, H0179:	l, H0188: 1, H0290: 1,	H0292: 1, H0252: 1, H0328:	l, S0368: 1, H0181: 1,	H0063: 1, H0264: 1, S0038:	10560: 1, H0625: 1,	64: 1, S0440: 1, H0130:	1, H0641: 1, H0646: 1,	S0344: 1, H0529: 1, L0369:	0371: 1, L0761: 1,	L0772: 1, L0800: 1, L0662:	0768: 1, L0364: 1,	L5568: 1, L0774: 1, L0523:	, L0653: 1, L0807: 1,	L0809; 1, L0647: 1, L0664:	1, S0052: 1, S0216: 1,
H01	HOZ		201	1, H	H07	1, S	HOS	1,T	008	1, H	H05	1, H	00H	H, 1	H02	1, S	00H	H, H	804	1, H	803	1,1	LO7	1,1	LSS	1, L		1, S
																-												

	1-18	5-26, 90- 108, 52-72
·		
H0144: 1, H0547: 1, H0670: 1, S0378: 1, S0152: 1, H0521: 1, S0206: 1, L0743: 1, L0740: 1, L0779: 1, L0731: 1, L0588: 1, L0608: 1, L0603: 1, H0653: 1, H0667: 1, H0216: 1, S0192: 1, S0194: 1 and S0196: 1.	AR033: 7, AR052: 2, AR089: 1, AR053: 1, AR061: 1, AR060: 1, AR055: 0, AR096: 0, AR104: 0, AR039: 0 L0769: 8, L0794: 8, L0439: 7, H0399: 3, L5565: 3, L0778: 3, H0253: 2, H0051: 2, L0438: 2, L0748: 2, L0777: 2, H0624: 1, H0441: 1, H0438: 1, L0021: 1, H0618: 1, S0049: 1, H0562: 1, S0050: 1, S0051: 1, L0638: 1, L0789: 1, H0547: 1, H0658: 1, L0743: 1, L0753: 1, S0031: 1 and S0260: 1.	AR096: 75, AR089: 75, AR039: 63, AR104: 56, AR053: 46, AR052: 36,
	Cys-30 to Tyr-36, Thr-41 to Gly-46, Val-111 to His-122, Pro-201 to Arg-206, Pro-209 to His-216.	Lys-45 to Arg-52.
	1578	1579
	375 - 1022	157 - 666
	173	174
	731889	732236
	HDFAB91	HWLER32
	163	164

	43-59
AR050: 31, AR033: 30, AR055: 11, AR061: 10 L0748: 3, S0354: 1, H0421: 1, H0355: 1, S0428: 1 and S0031: 1.	AR055: 9, AR052: 7, AR060: 4, AR033: 4, AR061: 4, AR089: 3, AR096: 3, AR053: 3, AR039: 1, AR104: 1 H0271: 11, L0759: 4, L0779: 3, L0755: 3, H0222: 2, H0575: 2, H0705: 2, H0581: 2, H0622: 2, H0030: 2, L0777: 2, L0591: 2, H0556: 1, H0159: 1, H0556: 1, H0437: 1, T0060: 1, H0650: 1, S0418: 1, S0045: 1, H0179: 1, H0046: 1, L0163: 1, S0051: 1, H0628: 1, S0366: 1, H0038: 1, H0551: 1, H0488: 1, H0268: 1, R0599: 1, H0038: 1, H0551: 1, H0488: 1, H0268: 1, H0551: 1, H0529: 1, L0770: 1, L0667: 1, L0800: 1, L0641: 1, L0773:
	Gln-2 to Lys-7, Glu-35 to Thr-42, Arg-64 to Ser-72.
	1580
	29 - 430
	175
	732600
	HNFJE71
	165

	103-119, 63-79	86-103, 30-46
1, L0662: 1, L0794: 1, L0766: 1, L0650: 1, L0375: 1, L0530: 1, L0791: 1, L0663: 1, S0216: 1, S0380: 1, H0521: 1, S0027: 1, L0748: 1, L0731: 1, L0757: 1, L0758: 1 and H0423: 1.	AR033: 6, AR104: 2, AR060: 1, AR052: 1, AR089: 1, AR061: 0, AR055: 0, AR039: 0, AR096: 0, AR053: 0	AR060: 6, AR033: 6, AR055: 6, AR089: 5, AR096: 5, AR104: 5, AR052: 3, AR053: 3, AR061: 3, AR039: 1 H0399: 4, L0805: 3, H0661: 2, S0356: 2, H0457: 2, L0794: 2, L0775: 2, L0663: 2, L0747: 2, L0759: 2, L0005: 1, H0580: 1, S0222: 1, H0156: 1, L0021: 1, H0575: 1, H0123: 1, H0012: 1, H0057: 1, S0051: 1, H0328: 1, H0163: 1, H0038: 1, H0413: 1, H0100: 1,
	Phe-6 to Ser-16.	Phe-70 to Val-76.
	1581	1582
	536	- 248 248
	176	177
	732902	733800
	ноина 56	HMSHT01
	166	167

	50-66, 70- 86	194-211, 73-89	62-78, 20-
S0002: 1, L0598: 1, L0769: 1, L0766: 1, L0657: 1, L0666: 1, L0665: 1, H0435: 1, S0152: 1, H0521: 1, L0740: 1, L0754: 1, L0777: 1, S0194: 1, S0276: 1 and H0542: 1.	AR055: 9, AR061: 8, AR033: 6, AR052: 6, AR060: 5, AR089: 4, AR053: 4, AR096: 2, AR039: 1, AR104: 1 H0351: 2, H0575: 2, L0794: 2, L0803: 2, L0751: 2, H0333: 1, H0390: 1, H0553: 1, L0645: 1, L0766: 1, L0439: 1, L0747: 1, L0749: 1 and L0601: 1.	AR055: 4, AR033: 3, AR096: 3, AR052: 3, AR061: 3, AR039: 2, AR060: 2, AR089: 2, AR053: 1, AR104: 1 L0783: 2, L0751: 2, H0409: 1, H0559: 1, L0471: 1, H0646: 1, H0658: 1, S0390: 1, L0777: 1, L0731: 1 and L0462: 1.	AR096: 8, AR053: 7,
	Arg-16 to Glu-27.	1584 Pro-5 to Thr-10, Lys-23 to Asn-33, Gln-105 to Tyr-115.	1585 Glu-40 to Tyr-45.
	1583	1584	-
	96 - 401	880	35 - 673
	178	179	180
	734582	735584	735747
	HAPQM57	HSLJK58	HSLHL67
	168	169	170

36, 111- 127	98-116, 136-152	
		•
7 6, 1, 4, 5, 1	5, 6, 6, 6, 6, 7, 7, 6, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7,	
AR060: 7, AR039: 6 AR089: 6, AR052: 6 AR055: 6, AR104: 5 AR033: 5, AR061: 4 S0280: 1, H0488: 1, H0509: 1 and S0028: 1	AR055: 10, AR060: 7, AR033: 6, AR061: 6, AR033: 6, AR061: 6, AR089: 6, AR052: 4, AR104: 3, AR039: 2 H0052: 5, L0748: 5, L0756: 4, L0731: 4, S0360: 3, L0764: 3, L0747: 3, L0749: 3, H0255: 2, H0333: 2, L0055: 2, L0653: 2, L0740: 2, L0754: 2, L0750: 2, L056: 1, H0341: 1, H0662: 1, H0306: 1, H0402: 1, H0556: 1, H0434: 1, H0150: 1, L0770: 1, L0769: 1, L0630: 1, L0521: 1, L0662: 1, L0775: 1, L0776: 1, L0630: 1, L0521: 1, L0662: 1, L0775: 1, L0776: 1, L0630: 1, L0521: 1, L0662: 1, L0775: 1, L0776: 1, L0630: 1, L0521: 1, L0662: 1, L0775: 1, L0776: 1, L0630: 1, L0521: 1, L0529: 1, L0775: 1, L0776: 1, L0630: 1, L0521: 1, L0662: 1, L0775: 1, L0776: 1, L0630: 1, L0521: 1, L0662: 1, L0775: 1, L0776: 1, L0630: 1, L0521: 1, L0662: 1, L0775: 1, L0776: 1,	and S0242: 1.
AR060: AR089: AR055: AR033: S0280: H0509:	AR055: AR033: AR033: AR063: AR063: AR104: L0749: 3, L0749: 3, L0749: 2, L0556: 11, H0306 H0413: 1, L0779: L0493: 1, L0775: 1, S0044: L0752: 1, L07	1 and
·	Arg-11 to Ser-24, Ser-37 to Ala-43.	
	1586	
	1148	
	181	
	738228	
	HCEMF51	
	171	

83-102, 10-26	48-64, 121-137	47-67
AR089: 17, AR060: 15, AR096: 15, AR055: 13, AR039: 13, AR033: 12, AR104: 11, AR052: 10, AR053: 8, AR061: 7	AR061: 3, AR052: 2, AR089: 2, AR055: 2, AR033: 2, AR104: 2, AR096: 2, AR060: 1, AR053: 1, AR039: 0 L0742: 4, H0484: 2, L0763: 2, L0758: 2, H0483: 1, H0618: 1, H0047: 1, H0188: 1, S0344: 1, L0637: 1, L0771: 1, L0803: 1, L0628: 1, H0683: 1, H0522: 1 and L0752: 1.	AR089: 9, AR060: 8, AR033: 7, AR096: 2, AR053: 1, AR061: 1, AR055: 0, AR052: 0, AR039: 0, AR104: 0 L0809: 3, H0442: 2, S0010: 2, L0794: 2, L0803: 2, S0378: 2, H0341: 1, S0376: 1, H0611: 1, H0486: 1, H0013: 1, H0156: 1, L0021: 1, H0318: 1, H0123:
,	Ser-22 to His-33, Pro-85 to Asn-94, Phe-101 to Gln-108.	Ala-9 to Leu-16.
1587	1588	1589
182 59 - 373	129 - 656	149 - 526
182	183	184
738569	738911	739003
172 HTHCV59 738569	HCHCI12	HOEAU34
172	173	174

	71-90, 13- 29, 42-58	61-78
·		133780, 266150, 276903, 276903, 276903
		11q13.5
1, H0024: 1, L0483: 1, H0135: 1, H0163: 1, S0344: 1, L0769: 1, L0773: 1, L0774: 1, L0518: 1, S0126: 1, H0684: 1, S0380: 1, S0454: 1, H0436: 1, L0754: 1, L0747: 1, L0608: 1, S0026: 1, H0667: 1 and H0543: 1.	AR104: 1, AR061: 1, AR060: 0, AR039: 0, AR033: 0, AR089: 0 L0794: 3, L0749: 2, L0731: 2, H0650: 1, S0408: 1, S0300: 1, L0456: 1, L0769: 1, L0637: 1, L0643: 1, L0650: 1, L0666: 1, L0438: 1, H0696: 1 and L0747: 1.	AR055: 6, AR096: 5, AR052: 5, AR060: 4, AR089: 4, AR061: 4, AR053: 4, AR033: 3, AR104: 1, AR039: 0 L0362: 20, L0766: 11, L0754: 10, L0747: 5, L0731: 4, S0003: 3, H0547: 3, S0026: 3, S0212: 2, H0251: 2, H0046: 2, H0031:
		Lys-5 to Glu-11, Tyr-17 to Asp-25.
	1590	1591
	45 - 368	152 - 490
	185	186
	739048	739503
	HFASN59	176 HLHCU82
	175	176

		46-68, 21- 42, 66-82,
2, H0674: 2, L0769: 2, L0663: 2, L0665: 2, H0144: 2, L0438: 2, L0748: 2, L0439: 2, H0445: 2, H0170: 1, H0686: 1, T0049: 1, S0134: 1, H0657: 1, S0001: 1, H0459: 1, S0360: 1, S0280: 1, H0196: 1, H0596: 1, H0565: 1, H0571: 1, H0565: 1, H0024: 1, H0275: 1, H0565: 1, H0571: 1, H0565: 1, H0799: 1, L0649: 1, L0640: 1, L0779: 1, L0640: 1, L0774: 1, L0649: 1, L0803: 1, L0804: 1, L0642: 1, L0661: 1, L0642: 1, L0774: 1, L0666: 1, L0774: 1, L0666: 1, L0774: 1, L0666: 1, L0779: 1, L0758: 1, S0434: L0779: 1, L0758: 1, S0434: L0779: 1, L0758: 1, S0434:	1, LU589: 1, SU106: 1, H0667: 1 and S0424: 1.	AR096: 9, AR053: 9, AR052: 7, AR089: 6,
		1592 Ala-87 to Ala-97.
·		1592
		2615 - 2247
		187
		740786
		HSDJN50
		177

WO 01/90304		
2-18		89-106, 40-56
		
AR104: 4, AR060: 3, AR039: 3, AR055: 3, AR061: 2, AR033: 1 L0005: 4, S0045: 4, S0222: 4, S0028: 4, H0624: 3, S0144: 2, S0260: 2, S0134: 1, S0218: 1, H0381: 1, H0341: 1, S0001: 1, S0282: 1, S0046: 1, L0476: 1,	H0191: 1, H0575: 1, S0050: 1, H0048: 1, H0135: 1, S0038: 1, H0100: 1, S0150: 1, L0378: 1, S0052: 1, S0044: 1, S0390: 1 and S0031: 1.	AR052: 11, AR053: 9, AR033: 7, AR096: 7, AR104: 6, AR089: 6, AR060: 4, AR055: 3, AR061: 2, AR039: 2 S0354: 5, S0426: 5, S0002: 3, S0278: 2, L0755: 2, L0751: 2, L0758: 2, L0539: 1, H0392: 1, H0592: 1, H0318: 1, L0041: 1, H0494: 1, S0144: 1, S0142: 1, S0344: 1, L0803: 1, L0804: 1, L0805: 1, L0776: 1, S0052: 1, S0428: 1, S0053: 1, H0144: 1, S0378: 1,
·		Ser-23 to Lys-37, Thr-61 to Pro-66.
		1593
		803
		188
		741055
		HMAFM05
		178 1

	61-78						73-89,	109-125													99-119						
	133780, 266150,	276903,	276903,	276903											_												
	11q13.5						19																				
H0555: 1 and H0478: 1.	AR053: 24, AR052: 19, AR096: 7, AR089: 3,	AR033: 2, AR039: 2,		AR055: 1, AR061: 1	H0486: 1 and H0494: 1.		AR096: 2, AR060: 1,	AR089: 1, AR104: 1,	AR033: 1, AR055: 0,	AR061: 0, AR052: 0,	AR039: 0, AR053: 0	L0766: 2, L0776: 2,	L0759: 2, T0002: 1, H0329:	1, H0604: 1, H0424: 1,	S0144: 1, L0800: 1, L0644:	1, L0662: 1, L0804: 1,	L0775: 1, L0806: 1, L0805:	1, L0659: 1, H0593: 1,	H0539: 1, H0521: 1, L0786:	1, L0731: 1 and L0601: 1.	AR104: 74, AR096: 39,	AR089: 34, AR039: 33,	AR033: 24, AR052: 23,	AR060: 23, AR053: 20,	AR055: 11, AR061: 6	S0010: 1, L0740: 1 and	L0752: 1.
	Lys-5 to Glu-11, Tyr-17 to Asp-25,	Lys-39 to Ile-45,	Val-81 to Leu-93,	Thr-100 to Phe-106,	Thr-117 to Glu-126,	Thr-128 to Gln-133.	Leu-44 to Glu-49,	Tyr-61 to Cys-68,	Glu-94 to Ile-108.												Pro-6 to Thr-21,	Asp-47 to Ile-57,					
	1594						1595														1596				•		
	139 - 555						19 - 483									·					112-	492		-			
	189						190											-			191						
	741128						741659	•													741921						
	HKAAA18						HISCL61														HAGDA61						
	179					-	180		-												181						

62-78, 92- 108	54-71, 133-149	55-71, 24- 40, 74-90
AR096. 5, AR089: 3, AR060: 3, AR033: 2, AR104: 2, AR052: 1, AR039: 1, AR053: 1, AR055: 1, AR061: 1 H0038: 3, L0439: 3, H0039: 2, L0740: 2, L0747: 2, L0756: 2, H0592: 1, H0318: 1, H0031: 1, H0644: 1, L0766: 1, L0774: 1, L0666: 1, L0438: 1, L0754: 1, L0779: 1, L0758: 1, S0192: 1, S0194: 1 and H0506: 1.	AR033: 9, AR089: 4, AR052: 3, AR096: 3, AR053: 3, AR055: 3, AR060: 3, AR104: 2, AR061: 1, AR039: 1 L0748: 2, H0581: 1, H0046: 1, L0483: 1, H0634: 1, H0412: 1, S0150: 1, H0520: 1, L0612: 1 and H0520: 1, L0612: 1 and	AR033: 7, AR060: 5, AR089: 5, AR061: 2, AR039: 2, AR096: 1, AR055: 0, AR053: 0, AR052: 0
1597 Met-1 to Gly-7, Ala-16 to Gln-21, Ser-35 to Gly-41, Thr-43 to Asn-52.	Glu-4 to Gly-12, Gly-19 to Ser-37, Gln-49 to Asn-54, Glu-102 to Cys-108, Leu-116 to Asn-125.	Ser-43 to Val-53.
1597	1598	1599
535 - 209	46 - 840	101 - 442
192	193	194
742518	742690	743383
HFIIO11	HUSGB32	HTXED15
182	183	184

	75-91	128-146, 21-37, 63- 79	96-124
		601843	108725, 120700, 133171, 136836, 145981, 147141,
		19p12	19p13.3
H0265: 1, H0556: 1, H0026: 1, L0522: 1, L0665: 1 and H0445: 1.	AR052: 3, AR089: 2, AR033: 2, AR053: 2, AR060: 2, AR055: 1, AR096: 1, AR104: 1, AR061: 1, AR039: 0 H0521: 2, H0305: 1, H0046: 1, S0144: 1, S0002: 1, H0478: 1, L0748: 1, H0543: 1, H0423: 1 and H0542: 1.	AR055: 20, AR039: 13, AR052: 13, AR053: 11, AR061: 11, AR096: 10, AR033: 10, AR089: 9, AR060: 9, AR104: 7 H0428: 2, H0135: 2, L0794: 2, L0779: 2, L0770: 1, L0766: 1, L0774: 1, L0789: 1, L0792: 1, L0439: 1, L0731: 1 and L0757: 1.	AR053: 1, AR096: 1, AR055: 1, AR052: 1, AR089: 1, AR033: 1, AR061: 1, AR060: 1, AR104: 0, AR039: 0 L0747: 5, L0809: 3,
	·		1602 Gly-14 to Gly-23.
	1600	1601	1602
	25 - 333	55 - 573	201 - 611
	195	196	197
	743426	744278	744330
	HCFMF12	HSSJG62	нгінг63
	185	186	187

	115-131	71-99, 22-
164953, 188070, 600957, 601238, 601846, 602216,		
L0731: 3, L0759: 3, L0777: 2, L0752: 2, L0021: 1, S0250: 1, H0252: 1, L0770: 1, L0774: 1, L0792: 1, L0793: 1, L0758: 1 and S0194: 1.	AR033: 1, AR089: 0, AR061: 0, AR096: 0, AR060: 0, AR053: 0, AR104: 0, AR052: 0, AR055: 0, AR039: 0 L0372: 2, L0748: 2, L0439: 2, L0751: 2, L0754: 2, L0750: 2, L0756: 2, L0779: 2, L0756: 2, L0779: 1, R0282: 1, H0346: 1, S0376: 1, S0360: 1, T0040: 1, H0253: 1, H0424: 1, H0553: 1, H0674: 1, L0772: 1, L0764: 1, L0771: 1, L0803: 1, L0776: 1, L0659: 1, H0144: 1, S0374: 1 and L0747: 1.	AR096: 1, AR089: 1, AR033: 1, AR039: 0, AR061: 0, AR053: 0, AR104: 0, AR060: 0, AR052: 0, AR055: 0
	Tyr-9 to Asn-15, Arg-57 to Trp-64, Pro-68 to Ala-78, Gln-83 to Asp-88, Pro-106 to Ser-112.	
	1603	1604
	759 -	234 - 584
	198	199
	744453	744616
	188 HMDAG54 744453	HCHMI51
	188	189

23.	3,	0,	L0439:	7,	L0664:	6,	S0358:	5,	L0742:	5,	L0662:	4,	S0026:	3,	H0083:	3,	S0126:	3,	L0588:	2,	H0497:	2,	H0135:	2,	T0967:	2,	T0167:	2,	H0520:
H0046: 57, L0665: 23,	L0666: 15, L0777: 1.	L0752: 11, L0471: 10,	L0749: 9, L0759: 9, L0439:	8, L0747: 8, H0648:	L0753: 7, L0776: 6,]	6, H0435: 6, L0750: 6,	L0757: 6, L0593: 6,	5, L0769: 5, L0768: 3	L0375: 5, H0547: 5, L0742:	5, L0592: 5, L0595: 5,	L0455: 4, L0770: 4, L0662:	4, L0663: 4, L0758: 4,	L0590: 4, L0608: 4, S0026:	4, S0424: 4, H0624: 3,	H0556: 3, H0013: 3, H0083:	3, H0529: 3, L0774: 3,	L0657: 3, L0659: 3, S0126:	3, H0684: 3, H0659: 3,	L0740: 3, L0755: 3,]	3, L0591: 3, H0484: 2,	L0717: 2, H0550: 2, H0497:	2, H0333: 2, H0615: 2,	H0428: 2, H0068: 2, H0135:	2, H0038: 2, H0040: 2,	S0422: 2, L0638: 2, L0667:	2, L0372: 2, L0771: 2,	L0648: 2, L0363: 2, L0767:	2, L0388: 2, L0775: 2,	L0809: 2, S0374: 2, H0520:
											-																		
				7																									

			-							•																	
2, H0519: 2, S0152: 2,	H0555: 2, S0027: 2, L0748:	L. LU /45: 2, 50456: 2, L0599: 2, L0362: 2, H0506:	2, H0170: 1, H0171: 1,	50342: 1, 50430: 1, 50400: 1, H0661: 1, H0663: 1,	H0664: 1, H0450: 1, S0356:	1, S0376: 1, S0360: 1,	H0351: 1, H0411: 1, H0431:	1, H0370: 1, H0415: 1,	T0040: 1, L0021: 1, H0599:	1, H0575: 1, S0346: 1,	S0049: 1, H0052: 1, H0251:	1, H0050: 1, H0012: 1,	H0024: 1, H0057: 1, H0373:	1, L0163: 1, S0025: 1,	H0188: 1, H0328: 1, T0006:	1, H0553: 1, H0628: 1,	H0316: 1, H0090: 1, H0591:	1, H0551: 1, T0067: 1,	H0264: 1, H0412: 1, L0351:	1, L0564: 1, H0625: 1,	S0440: 1, H0509: 1, H0647:	1, H0652: 1, H0538: 1,	L0369: 1, L0520: 1, L0631:	1, L0796: 1, L0641: 1,	L0764: 1, L0389: 1, L0803:	1, L0378: 1, L0806: 1,	L0805: 1, L0652: 1, L0654:
			-																								
											,			***													

	84-100	76-107, 1- 17, 114-
	÷	
1, L0540: 1, L0383: 1, L0790: 1, L4508: 1, H0658: 1, H0650: 1, H0672: 1, H0651: 1, S0330: 1, S0378: 1, S0332: 1, S0013: 1, H0696: 1, S0392: 1, H0627: 1, H0445: 1, H0667: 1, H0542: 1, S0452: 1, L0600: 1 and H0352: 1.	AR052: 29, AR104: 27, AR056: 27, AR060: 22, AR053: 22, AR055: 11, AR059: 11, AR061: 9 H0599: 5, H0575: 3, L0438: 2, S0212: 1, S0420: 1, S0356: 1, H0393: 1, H0549: 1, H0391: 1, H0036: 1, T0071: 1, H0581: 1, S0051: 1, H0266: 1, H0271: 1, H0292: 1, H0272: 1, L0435: 1, H0280: 1, H0561: 1, H0599: 1, L0762: 1, H0547: 1, H0435: 1, H0521: 1, S0028: 1, L0439: 1, H0542: 1, H0543: 1 and H0542: 1,	AR039: 12, AR096: 7, AR104: 7, AR033: 6,
		Ser-21 to Trp-28, Arg-63 to Val-68.
	1605	1606
	531 531	108 -
	200	201
	744726	744831
	НАНЕА63	HAJAN63
·	190	191

130	256-273, 42-58
, , , , , , , , , , , , , , , , , , ,	5, , ,)764:)0013: 804:
AR060: 5, AR089: 4, AR052: 4, AR053: 4, AR055: 4, AR061: 3 H0616: 3, L0748: 3, L0756: 3, H0586: 2, H0356: 2, L0766: 2, L0803: 2, H0672: 2, L0439: 2, L0758: 2, L0465: 2, H0497: 1, H0013: 1, H0046: 1, L0471: 3, H0024: 1, S0214: 1, H0124: 1, H0561: 1, L0774: 4, L064: 1, L0438: 1, H0520: 1, H0519: 1, H0658: 3, L0664: 1, L0438: 1, H0539: 1, H0631: 1, H0595: 1, S0192: 1, H0595: 1, S0192: 1,	AR055: 10, AR060: 5, AR053: 5, AR052: 5, AR033: 5, AR061: 4, AR089: 4, AR096: 4, AR104: 2, AR039: 0 S0022: 7, L0805: 3, H0556: 2, H0046: 2, L0764: 2, L0662: 2, S0126: 2, AR050: 1, H0615: 1, H0039: 1, H0640: 1, H0087: 3, T0042: 1, L0643: 1, L0794: 1, L0803: 1, L0804:
AR060: 5, AR089: 4, AR052: 4, AR053: 4, AR055: 4, AR061: 3 H0616: 3, L0748: 3, L0756: 3, H0586: 2, H0356: 2, L0766: 2, L0803: 2, H0672: 2, L0439: 2, L0758: 2, L0465: 2, H0497: 1, H0013: 1, H0046: 1, L0471: 1, H0024: 1, S0214: 1, H0124: 1, H0561: 1, L0774: 1, L0664: 1, L0438: 1, H0520: 1, H0631: 1, L0740: 1, L0747: 1, L0755: 1, L0595: 1, S0192: 1,	AR055: 10, AR060: 5, AR053: 5, AR052: 5, AR033: 5, AR061: 4, AR089: 4, AR096: 4, AR104: 2, AR039: 0 S0022: 7, L0805: 3, H0556: 2, H0046: 2, L0764: 2, L0662: 2, S0126: 2, L0748: 2, H0305: 1, H0013: 1, H0050: 1, H0615: 1, H0039: 1, H0040: 1, H0087: 1, T0042: 1, L0643: 1, L0794: 1, L0803: 1, L0804:
	38, 44, 38, 33, 38, 38, 38, 38, 38, 38, 38, 38
	Pro-27 to Arg-42, Asp-94 to Ser-104, Arg-114 to Asn-120, Ala-127 to Ala-138, Ala-156 to Pro-163, Gln-231 to Leu-238.
	1607
	368 - 1276
	202
	745408
	HSRFP52
	192

	<u></u>	
	177-195, 53-69, 150-166, 16-32	
1, H0547: 1 and	2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	1,
1, L0807: 1, L0809: 1, L0666: 1, H0144: 1, H0547: 1, L0749: 1, L0779: 1 and L0758: 1.	AR104: 10, AR033: 7, AR096: 5, AR089: 4, AR052: 3, AR053: 3, AR052: 1, AR060: 3, AR055: 1, AR061: 1 S0001: 4, L0439: 4, H0617: 3, L0776: 3, L0438: 3, L0748: 3, H0484: 2, S0420: 2, S0222: 2, H0274: 2, H0181: 2, H0529: 2, L0517: 2, L0789: 2, H0659: 1, H0656: 1, S0418: 1, L0005: 1, S0476: 1, H0645: 1, H0656: 1, S0418: 1, H0038: 1, H0052: 1, H0597: 1, H0673: 1, S0036: 1, H0078: 1, H0494: 1, L0769: 1, L0796: 1, L0372: 1, L0800: 1, L0643: 1, L0645: 1, L0800: 1, L0643: 1, L0645: 1, L0800: 1, L0768: 1, L0800:	1, L0805: 1, L0792: 1,
1, L0807: L0666: 1, 1, L0749: L0758: 1.		1, L0805
	Gly-7 to Lys-16, Gly-84 to Pro-90, Pro-100 to Ser-106.	
	1608	
	140 - 904	
	203	
	746390	
	нснон38	
	193	

	201-217
4: 1, H0547: 696: 1, 8: 1, S0032: 754: 1, 7: 1, L0780: 592: 1, 6: 1 and	(053: 10, 055: 7, 060: 5, 061: 4, 104: 4, 457: 9, 3: 7, L0731: 770: 4, 2: 4, S0002: 445: 3, 2: 3, H0423: 575: 2, 7: 2, L0646: 655: 2, 9: 2, L0594: 6: 1, S0222: 635: 1, 6: 1, S0272: 635: 1, 6: 1, S0474: 1, S0474: 6: 1, S0474: 1, S0474: 1, S0474: 1, S047
L0793: 1, S0374: 1, H0547: 1, S0328: 1, H0696: 1, S0406: 1, S0028: 1, S0032: 1, L0742: 1, L0779: 1, L0777: 1, L0779: 1, L0777: 1, L0780: 1, L0757: 1, L0592: 1, L0595: 1, S0026: 1 and H0423: 1.	AR052: 11, AR053: 10, AR096: 9, AR055: 7, AR033: 6, AR060: 5, AR039: 5, AR061: 4, AR089: 4, AR104: 4 L0748: 14, H0457: 9, L0766: 8, H0543: 7, L0731: 6, L0439: 5, L0770: 4, L0747: 4, H0542: 4, S0002: 3, L0777: 3, H0445: 3, S0134: 3, S0192: 3, H0423: 4, S0114: 2, H0575: 2, S0010: 2, L0667: 2, L0646: 2, L0775: 2, L0655: 2, H0436: 2, L0749: 2, L0594: 2, H0422: 2, S0342: 1, S0134: 1, H0583: 1, S0212: 1, S0376: 1, S0476: 1, S0247: 1, H0486: 1, H0635: 1, H0156: 1, S0346: 1, S0474:
고 , 오 , 그 도	Thr-17 to Glu-25, A Glu-61 to Val-66, A Leu-122 to Cys-129, A Glu-139 to Asp-148, A Pro-169 to Val-179, A Lys-183 to Gly-193. Lys-183 to Gly-193. Lys-184 to Gly-195. Sign of the color of
	1609
	783 - 1
	204
	746583
	HMSBS61
	194

	180-197
H0050: 1, H0687: 1, S0214: 1, L0483: 1, H0032: 1, S0364: 1, L0455: 1, H0708: 1, H0591: 1, H0647: 1, H0647: 1, H0529: 1, L0761: 1, L0771: 1, L0662: 1, L0803: 1, L0650: 1, L0774: 1, L0805: 1, L0776: 1, L0659: 1, L0540: 1, L0778: 1, L0789: 1, L0790: 1, L0793: 1, L0665: 1, H0144: 1, H0547: 1, H0672: 1, H0539: 1, S0152: 1, L0750: 1, L0757: 1, L0758: 1, S0308: L0757: 1, L0758: 1, S0308: L0757: 1, L0758: 1, S0308:	1610 Met-1 to Ser-7. AR055: 9, AR060: 5, AR052: 5, AR061: 4, AR033: 4, AR096: 3, AR053: 3, AR099: 3, AR104: 1, AR039: 1 H0521: 3, L0731: 3, H0591: 2, H0436: 2, H0422: 2, H0170: 1, S0046: 1, S0476: 1, H06459: 1, S0046: 1, S0476: 1, H0650: 1, H0699: 1, H0635: 1, L0747: 1, S0434: S0152: 1, L0747: 1, S0434:
	908
	205
	746584
	HNFHK32
	195

	106-122									109-125,	6-22					62-96, 17-	48, 89-105					112-128,	56-72			
											_															
1, L0601: 1, H0542: 1 and H0543: 1.	AR053: 21, AR052: 15, AR096: 13, AR089: 12,	AR060: 10, AR055: 9,	AR033: 9, AR104: 7,	8061: 6, AR039: 6	H0486: 2, L0747: 2,	S0298: 1, H0392: 1, T0010:	H0039: 1, H0529: 1,	L0766: 1, L0438: 1, L0731:	1, L0591: 1 and H0543: 1.	AR089: 1, AR096: 0,	AR060: 0, AR052: 0,			AR039: 0	H0013: 2 and S0218: 1.		AR052: 6, AR060: 5,	4, AR061:	AR033: 4, AR039: 3,	AR089: 3, AR104: 3	H0040: 2		AR061: 9, AR033: 8,	AR104: 8, AR096: 7,	AR089: 6, AR053: 5,	AR052: 4, AR039: 4
1, HC	Tyr-14 to Glu-19, AI Lys-48 to Asp-91. AI		AI	AI	四	0 <u>S</u>	1,	<u>n</u>	11,	AF	AF	AI	AF	AI	H	AF	AI	AI	AI	AF		4 Cys-175 to Val-181, AF			Lys-233 to Phe-242. AF	AF
	- 556 1611		·							- 72 1612						7 - 1613					_	161				
	206 53 -									207 470 - 72	<u> </u>					208 117 -	43	_				209 2 - 751		-		
	747208			············						750243			-			750750						751048				
	HTPCT63					-				HE8NL29			····			HTTFM66				_		HE9EM20				
	196									197						198						199				

	193-218, 30-46
L0803: 8, L0748: 7, L0759: 5, L0588: 3, H0489: 2, L0105: 2, L0659: 2, L0666: 2, H0144: 2, H0520: 2, H0547: 2, L0754: 2, L0754: 2, L0747: 2, L0756: 2, L0752: 2, S0360: 1, L0717: 1, H0611: 1, H0333: 1, H0046: 1, T0010: 1, H0428: 1, H0039: 1, T0023: 1, H0031: 1, H0553: 1, H0644: 1, S0366: 1, H0652: 1, L0372: 1, L0666: 1, L0774: 1, L0775: 1, L0662: 1, L0804: 1, L0774: 1, L0775: 1, L0779:	AR096: 12, AR089: 9, AR033: 5, AR052: 5, AR039: 5, AR060: 4, AR104: 3, AR053: 2, AR061: 1, AR055: 1 S0410: 4, H0660: 4, S0354: 2, H0370: 2, L0662: 2, L0438: 2, L0748: 2, H0664: 1, S0360: 1, H0208:
	Lys-12 to Glu-27, Pro-48 to Lys-56.
	1615
	832
	210
	751286
	HISCQ44
	200

	175-192, 94-110
1	
	·
1, H0574: 1, H0575: 1, H0590: 1, L0040: 1, H0051: 1, H0169: 1, H0674: 1, H0412: 1, L0645: 1, L0767: 1, L0666: 1, L0665: 1, H0547: 1, H0539: 1, H0478: 1, L0611: 1, L0741: 1, L0750: 1 and S0434: 1.	AR055: 8, AR053: 6, AR052: 6, AR033: 6, AR060: 5, AR089: 5, AR039: 3, AR104: 3 H0551: 3, H0529: 3, L0770: 3, L0769: 3, L0794: 3, L0778: 3, S0418: 2, L0773: 2, L0521: 2, H0701: 2, S0126: 2, L0747: 2, L0731: 2, L0521: 2, H0295: L0731: 2, L056: 1, H0295: 1, S0134: 1, H0556: 1, H0592: 1, S0134: 1, H0535: 1, H0661: 1, S0476: 1, H0592: 1, H0013: 1, H0635: 1, H0581: 1, S0250: 1, H0212: 1, H0412: 1, S0438: 1, S0440: 1, S0144: 1, L0763: 1, L0645: 1, L0764: 1, L0766: 1, L0775: 1, L0783: 1, L0665: 1, H0519: 1,
	Ala-10 to Glu-18, Arg-26 to Arg-31, Phe-48 to Gln-53, Gly-77 to Glu-84, Met-130 to Gly-138, Tyr-225 to Ala-232. I
	203 - 1616 961
	677 211
	HTGAU79 751677
	201

<u> </u>		
	69-103, 90-106, 1- 17	<i>57-</i> 76, 114-130
5:		3 3 1 G 3
H0435: 1, H0672: 1, H0436: 1, S3014: 1, S0028: 1, L0750: 1, L0777: 1, S0436: 1, L0366: 1, H0667: 1 and H0423: 1.	AR055: 3, AR033: 2, AR104: 2, AR060: 2, AR053: 2, AR039: 2, AR089: 1, AR061: 1, AR096: 1, AR052: 0 H0046: 2, H0431: 1, S0428: 1 and H0660: 1.	AR096: 8, AR052: 7, AR039: 6, AR053: 6, AR033: 5, AR089: 4, AR055: 4, AR104: 3, AR061: 3, AR060: 3 H0618: 9, L0751: 7, L0754: 6, L0758: 6, H0253: 5, L0748: 5, L0439: 5, H0580: 3, H0052: 3, L0770: 3, L0663: 3, H0556: 2, S0418: 2, H0733: 2, H0351: 2, H0706: 2, H0567: 2, L0659: 2, L0543: 2, L5623: 2, L0749: 2, S0436: 2, H0423: 2, H0381: 1, S0212: 1, H0254: 1, H0663:
H0435: 1 1, S3014: L0750: 1 1, L0366: H0423: 1		AR096: AR039: AR033: AR033: AR055: AR061: H0618: L0754: 6 5, L0748 H0580: 3 3, L0663 S0418: 2 2, H0706 H0625: 2 2, H0705 L5623: 2 2, H0423 S0212: 1
	Pro-26 to Pro-31, Pro-119 to Asp-124, Gln-132 to Leu-140, Arg-143 to Pro-149.	·
	1617	1618
	17 - 463	64 - 456
	212	213
	751735	752630
-	HETAJ12	HDABX16
	202	203

		110-136
		131400,
		5q31.1
1, H0638: 1, S0045: 1, S0046: 1, S0046: 1, S0476: 1, S6022: 1, H0549: 1, H0550: 1, S0222: 1, H0370: 1, H0497: 1, H0574: 1, L0622: 1, H0101: 1, H0427: 1, H0104: 1, H0101: 1, H0620: 1, H0104: 1, H0630: 1, H0570: 1, H0030: 1, H0628: 1, H0551: 1, H0628: 1, H0530: 1, H0551: 1, H0100: 1, L0351: 1, H0494: 1, S03438: 1, H0633: 1, S0422: 1, L0371: 1, L0772: 1, L0648: 1, L0497: 1, L0351: 1, L0375: 1, L0666: 1, H0144: 1, H0520: 1, H0553: 1, H0633: 1, H0633: 1, L0648: 1, L0511: 1, L0375: 1, L0375: 1, L0666: 1, H0144: 1, H0520: 1, H0553: 1, H0652: 1, H0662: 1, H0	1, H0732: 1, S3012: 1, S3014: 1, S0027: 1, S0028: 1, L0779: 1, L0584: 1, L0608: 1, L0593: 1, H0667:	AR033: 12, AR055: 11,
		Asp-20 to Glu-26,
•		1619
		27 - 458
		214
		753105
		HFEBM11
		204

	76-93, 38-	108-139	46-63
14761, 147575, 147575, 147575, 153455, 159000, 181460, 600807, 601596,			
AR089: 10, AR052: 9, AR061: 9, AR053: 8, AR060: 8, AR096: 4, AR039: 3, AR104: 0 H0081: 1, H0509: 1 and S0330: 1.	Ser-26 to Asn-35, AR052: 297, AR053: 285, Gly-95 to Pro-100, AR096: 212, AR039: 173, Arg-115 to Gln-126, AR089: 146, AR055: 106, Arg-132 to Asp-137, AR104: 92, AR060: 90, Val-183 to Ser-188. AR061: 69, AR033: 67 H0169: 4, L0529: 2, H0624: 1, H0341: 1, H0333: 1, H0013: 1, H0269: 1, S0440: 1, L0770: 1, L0809: 1, L0770: 1 and L0758: 1.	AR104:1068, AR061: 633, AR060: 627, AR055: 507, AR033: 469, AR089: 444, AR052: 279, AR039: 276, AR096: 237, AR053: 231 H0069: 5 and H0634: 1.	AR104: 18, AR033: 16, AR055: 9, AR060: 7,
Asp-48 to Tyr-57, A Asn-59 to Gly-66, A Ala-69 to Gly-76, A Ser-91 to Asn-97. Str. 91	Ser-26 to Asn-35, Gly-95 to Pro-100, Arg-115 to Gln-126, Arg-132 to Asp-137, Val-183 to Ser-188.	Ser-50 to Thr-55, Ser-67 to Asp-72, Ala-105 to Ser-110, Gln-139 to Lys-149, Arg-152 to Ser-166.	1622 Gly-15 to His-27, A Pro-35 to Ser-44. A
	979 - 1620 1584	456 - 1621 959	9 - 317 162
	215	216	217
	753235	753289	754184
	HHGBS74	нтаат39	HHSFO30
	205	206	207

	55-74, 88- 104	324-340, 235-251, 64-80, 344-360	100-130,
AR061: 7, AR052: 6, AR089: 6, AR053: 4, AR096: 4, AR039: 4 L0471: 1, S0388: 1, H0633: 1 and L0591: 1.	AR061: 6, AR096: 6, AR060: 6, AR089: 6, AR039: 6, AR033: 5, AR052: 5, AR055: 5, AR053: 4, AR104: 4 H0069: 3, L0794: 1, L0803: 1 and L0758: 1.	AR052: 11, AR096: 9, AR052: 8, AR089: 6, AR104: 6, AR089: 6, AR055: 4, AR039: 4, AR033: 4, AR061: 3 H0521: 2, H0170: 1, S0134: 1, H0662: 1, S0354: 1, H0580: 1, H0619: 1, S0278: 1, H0574: 1, H0599: 1, H0590: 1, H0596: 1, L0471: 1, H0024: 1, H0014: 1, L0163: 1, H0644: 1, H0551: 1, S0002: 1, H0658: 1, L0602: 1, H0522: 1, S3014: 1, L0731: 1, L0601: 1 and L0366: 1.	AR055: 10, AR089: 8,
	Lys-11 to Glu-29.	Asp-44 to His-54, Gly-92 to Lys-98, Gln-110 to Gly-115, Tyr-135 to Gly-140, Gly-162 to Ala-167.	
	1623	1624	1625
,	34 - 366	218 - 1390	337 -
	218	219	220
	754529	756579	756676
	HTAFE69	209 HMSCM47	HETLM70 756676
	208	209	210

· · · · · · · · · · · · · · · · · · ·	
1-21, 161- 192, 63- 80, 44-60	111-129, 95-111
AR052: 7, AR061: 7, AR062: 7, AR061: 7, AR060: 5, AR039: 5, AR096: 4, AR104: 3 L0803: 3, S0406: 3, H0356: 2, L0800: 2, L0517: 2, L0666: 2, L0751: 2, L0666: 2, L0751: 2, L0666: 1, S0442: 1, S0358: 1, S0444: 1, H0046: 1, H0150: 1, H0188: 1, H0674: 1, L0662: 1, L0774: 1, L0775: 1, L0805: 1, L0657: 1, L0775: 1, L0665: 1, H0689:	AR089: 5, AR052: 5, AR033: 4, AR052: 5, AR096: 3, AR061: 3, AR104: 2, AR060: 2, AR055: 2, AR039: 2 H0556: 4, H0169: 3, L0766: 3, L0742: 3, L0747: 3, S0360: 2, S0046: 2, H0587: 2, L0483: 2, T0006:
	Leu-64 to Ala-75.
	1626
1080	21 - 407
	221
	756950
	HLYEN32
	211

-	83-99, 111-127
2, H0488: 2, H0059: 2, L0646: 2, S0404: 2, L0748: 2, L0439: 2, L0751: 2, H0542: 2, H0265: 1, S0040: 1, H0341: 1, S0444: 1, S0045: 1, S0132: 1, S0222: 1, H0043: 1, H0043: 1, H0040: 1, H0052: 1, H0040: 1, H0052: 1, H0063: 1, H0063: 1, H0063: 1, H0063: 1, H00647: 1, S0002: 1, L0761: 1, L0771: 1, L0662: 1, L0762: 1, L0665: 1, H0644: 1, L0771: 1, L0664: 1, L0665: 1, H0644: 1, H0570: 1, H0559: 1, S0380: 1, H0539: 1, S0380: 1, H0539: 1, S0380: 1, H0539: 1, L0756: 1, L0756: 1, L0756: 1, L0750: 1, L0756: 1, L0750: 1, L0	2, AR089: 2, 1, AR060: 1, 0, AR039: 0,
2, H0488: 2, H0059: 2, L0646: 2, S0404: 2, L0748: 2, L0439: 2, L0751: 2, H0542: 2, H0265: 1, S0040: 1, H0341: 1, S0444: 1, S0045: 1, S0132: 1, S0222: 1, H00438: 1, S0132: 1, S0222: 1, H00438: 1, S01346: 1, H0052: 1, H0049: 1, H0059: 1, H0049: 1, H0059: 1, H0049: 1, H0647: 1, S0002: 1, L0761: 1, L0771: 1, L0662: 1, L0764: 1, L0665: 1, H0647: 1, L0664: 1, L0665: 1, H0648: 1, L0665: 1, H0648: 1, H0550: 1, H0519: 1, S0126: 1, H0696: 1, H0672: 1, H0518: 1, H0696: 1, H0673: 1, L0750: 1, L0758: 1, L0759: 1, L0759: 1, L0758: 1, L0759: 1, H0445: 1, S0436: 1, H0445: 1, S0446: 1,	1 and H0543: 1. AR033: 2, AR089: AR061: 1, AR060: AR096: 0, AR039:
	1627 Gly-9 to Leu-25.
	1627
	234 -
	222
	757207
	ннгн045
	212

	
	79-97
.: 6. 7. 6. 5. 6. 5. 6. 6. 6. 6. 6. 6. 6. 6. 6. 6. 6. 6. 6.	3:
8055: 0 758: 6, 48: 4, L0731: 3809: 3, 52: 3, L0759: 0486: 2, 50: 2, L0471: 0181: 2, 77: 2, L0666: 1116: 1, 8: 1, H0549: 3738: 1, 12: 1, H0622 3738: 1, 50: 1, L0769: 7768: 1, 50: 1, L0775: 655: 1, 7768: 1, 7768: 1, 7768: 1,	9, AR055: 6, 5, AR060: 4, 4, AR096: 4, 4, AR061: 4, 0 2, H0717: 1, S0442: 1, H025
AR053: 0, AR055: 0 L0794: 6, L0758: 6, L0805: 4, L0748: 4, L0731: 4, L0806: 3, L0748: 4, L0731: 4, L0806: 3, L0752: 3, L0759: 3, H0457: 2, H0486: 2, H0457: 2, H0150: 2, L0471: 2, H0620: 2, H0181: 2, S0002: 2, L0517: 2, L0666: 2, L0757: 2, S0116: 1, H0057: 1, L0738: 1, H0050: 1, L0738: 1, H0050: 1, L0769: 1, L0800: 1, L0763: 1, L0769: 1, L0776: 1, L0659: 1, L0751: 1, L0384: 1, H0144: 1, S0374: 1, H0547: 1, H0696: 1, L0439: 1, L0751: 1,	AR053: 9, AR055: 6, AR089: 5, AR060: 4, AR052: 4, AR096: 4, AR033: 4, AR061: 4, AR104: 0 H0050: 2, H0717: 1, S0420: 1, S0442: 1, H0253:
ARO LO 2 2 4 1 3 1 4 1 5 2 5 2 4 1 4 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	AR053: AR089: AR052: AR104: H0050 S0420:
	80
	162
	311 - 631
	223
	757351
	HHFHR59
	213

	156-172, 186-204, 85-101	59-76, 26- 42
1, H0052: 1, H0135: 1, H0063: 1, H0494: 1, L0794: 1, L0649: 1, S0037: 1, L0439: 1, L0747: 1, S0434: 1 and H0506: 1.	AR051: 1, AR096: 1, AR053: 0, AR089: 0, AR039: 0, AR055: 0, AR039: 0, AR060: 0, AR052: 0, AR104: 0 H0031: 3, L0806: 3, L0794: 3, L0666: 2, L0751: 2, H0265: 1, S0376: 1, H0559: 1, H0486: 1, H0156: 1, L0021: 1, H0599: 1, S0049: 1, L0761: 1, L0649: 1, L0803: 1, L0655: 1, L4507: 1, H0723: 1, H0593: 1, H0539: 1, H0522: 1, L0756: 1, L0779: 1, L0755: 1, L0796: 1 and H0506: 1.	AR053: 9, AR052: 8, AR089: 6, AR055: 5, AR033: 5, AR096: 4, AR060: 3, AR061: 3, AR039: 2, AR104: 1 H0638: 5, L0761: 4,
	Ser-63 to Glu-72, AR061: Asn-123 to Thr-130, AR053: Pro-209 to Pro-215. AR039: AR052: H0031: L0794: 3 2, H0265: 1 1, L0021 S0049: 1 1, L4507 H0593: 1 1, L4507 H0593: 1 1, L0756 L0755: 1 1, L0756	
	1629	1630
	891 891	87 - 437
	224	225
		757601
	HDPPA45	215 HMAGC74 757601
	214	215

WO 01/90304 PCT/US01/16450

	······································		
	<u> </u>		
		8: 5: 11:	&i ++ +: &i
H0556: 3, S0278: 2, H0013: 2, H0545: 2, H0622: 2, S0344: 2, S0002: 2, L0770: 2, L0769: 2, L0803: 2, L0774: 2, L0805: 2, L0789: 2, H0547: 2, H0521: 2, H0522: 2, H0187: 2, L0439:	2, L0740: 2, L0749: 2, L0758: 2, L0592: 2, H0159: 1, S0040: 1, S0114: 1, H0484: 1, H0255: 1, S0358: 1, H0619: 1, H0550: 1, H0559: 1, H0575: 1, H0618:	1, S0010: 1, H0052: 1, H0544: 1, H0546: 1, H0051: 1, H0252: 1, L0483: 1, H0030: 1, H0124: 1, H0135: 1, H0087: 1, L0351: 1, H0494: 1, H0561: 1, S0448: 1, H0641: 1, H0538: 1,	L0646: 1, L0800: 1, L0642: 1, L0773: 1, L0794: 1, L0804: 1, L0775: 1, L0784: 1, L0628: 1, L0659: 1, L0666: 1, L0664: 1, L0665: 1, H0144: 1, H0689: 1, H0682: 1, L0743: 1, L0748: 1, L0745: 1, L0759: 1, L0601: 1, S0192: 1 and L0698: 1.
22: 22: 22: 22: 23: 2, L. 23: 2, L. 22: 22: 22: 22: 22: 22: 2, L. 23: 23: 23: 23: 23: 23: 23: 23: 23: 23:	19. 2 2, H 2. 1, H 11, S 11, S 11, H	52: 1, F : 1, F 83: 1, F : 1, F : 1, S : 1, S	1, L 1, L 1, L 1, L 1, L 1, L 1, L 1, L
H0556: 3, S0278: 2, HC 2, H0545: 2, H0622: 2, S0344: 2, S0002: 2, LO 2, L0769: 2, L0803: 2, L0774: 2, L0805: 2, L0 2, H0547: 2, H0521: 2, H0522: 2, H0187: 2, LC	2, L0740: 2, L0749: 2, L0758: 2, L0592: 2, H(1, S0040: 1, S0114: 1, H0484: 1, H0555: 1, S(1, H0619: 1, H0575: 1, H0559: 1, H0575: 1, H0559: 1, H0575: 1, H0579: 1, H05	1, S0010: 1, H0052: 1 H0544: 1, H0546: 1, F I, H0252: 1, L0483: 1 H0030: 1, H0124: 1, F I, H0087: 1, L0351: 1 H0494: 1, H0561: 1, S I, H0641: 1, H0538: 1	LO646: 1, LO800: 1, LO 1, LO773: 1, LO794: 1, LO804: 1, LO775: 1, LO 1, LO628: 1, LO659: 1, LO666: 1, LO664: 1, LO 1, HO144: 1, HO689: 1, HO682: 1, LO743: 1, LO 1, LO745: 1, LO759: 1, LO601: 1, S0192: 1 and LO698: 1.
3, SC 5, 2, SC 7, 1, C 7, 1, C 7, 1, C	7, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	.; ;; ;; ;; ;; ;; ;; ;; ;; ;; ;; ;; ;; ;	;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;
56: 74: 74: 74: 72: 72: 72: 72: 72: 72: 72: 72: 72: 72	0740 0040 84: 0619 59:	9010 44: 0255 30: 9087 94:	, L0773 , L0773 , L0628 , L0628 , H014 , H0144 , L0745 , L0745
H05 2, H 2, L 2, L 1, H 105 H05	2, L L07 1, S H04 H, H	1, S HO5 1, H HO0 H, H HO4	L06 1, L 1, L 1, L 1, L 1, L 1, L
		·	
		· · · · · · · · · · · · · · · · · · ·	

WO 01/20304	1 € 1/6501/10450
238-254	259-293, 138-159, 36-57, 102-127, 235-252, 70-86, 325-341
AR053: 4, AR052: 4, AR055: 4, AR089: 3, AR089: 3, AR033: 3, AR060: 3, AR039: 0 H0657: 2, H0485: 2, L0163: 2, L0766: 2, L0764: 2, L0766: 2, L0754: 2, L0756: 2, L0766: 2, L0754: 2, L0756: 2, L0759: 2, L0756: 2, L0759: 1, H0659: 1, H0644: 1, L0142: 1, H0628: 1, S0438: 1, H0509: 1, S0422: 1, L0665: 1, L0665: 1, L0382: 1, L0655: 1, L0665: 1, L0794: 1, L0596: 1, S0106: 1, S0146: 1, S0242: 1, H0543: 1 and S0424: 1.	AR055: 6, AR060: 4, AR061: 3, AR089: 3, AR033: 3, AR052: 2, AR053: 2, AR096: 2, AR104: 2, AR039: 1 S0376: 1, H0580: 1, H0614: 1, H0284: 1, H0268:
1631 Ser-51 to Phe-57.	Lys-7 to Pro-14.
	1632
37 - 813	162 - 1289
226	727
759851	759888
216 HHFFR79 759851	217 HMGBP83
216	217

WO 01/90304

	7-37, 31- 51, 67-90, 105-121	72-101, 32-53	<i>57-73</i> , 4-20	103-119
1, H0412: 1, H0623: 1, T0042: 1, S0126: 1, H0539: 1, H0521: 1 and L0779: 1.	AR061: 6, AR055: 4, AR039: 3, AR033: 3, AR039: 3, AR052: 3, AR089: 3, AR096: 2, AR053: 1, AR104: 1 L0749: 5, L0752: 5, L0748: 4, H0510: 2, S0440: 2, L0800: 2, S0436: 2, H0294: 1, H0393: 1, L0803: 1, L0774: 1, L0383: 1, L0789: 1 and L0779: 1.	AR039: 6, AR053: 4, AR089: 3, AR104: 3, AR096: 3, AR052: 3, AR033: 2, AR055: 2, AR060: 2, AR061: 2 H0580: 1 and L0601: 1.	AR039: 25, AR096: 18, AR089: 18, AR053: 12, AR060: 11, AR104: 11, AR052: 10, AR033: 10, AR055: 6, AR061: 3 S0050: 1 and H0555: 1.	AR089: 1, AR060: 1, AR033: 1, AR053: 0, AR039: 0, AR096: 0,
	Phe-60 to Gly-67.			Met-1 to Glu-9, Ser-18 to Ile-26.
	1633	1634	1635	1636
	179 - 574	90 - 392	146 - 457	20 - 460
	228	229	230	231
	760121	760146	760240	760321
	HAUBV24	HWBAQ71	HRACE71	HADGC71
	218	219	220	221

·	
	82-107
-	
	5222: 126: 556: 5599: 596: 531: 551:
AR061: 0, AR052: 0, AR104: 0, AR055: 0 H0427: 1 and H0328: 1	7, AR096; 6, 4, AR055; 4, 3, AR104; 2, 2, AR039; 1; 5, H0543; 5, 4, H0170; 4, S023; 3, 3, S0003; 3, 3, H0519; 3, T0041; 1, H055; 2, S0422; 2, S0422; 2, S0422; 2, S0422; 2, H0571; 1, H056; 1, H0579; 1, L0779; 1, H0579; 1, L0779; 1, H0579; 1, L0779; 1, H0579; 1, L0779; 1, L0779
AR061: 0, AR052: 0 AR104: 0, AR055: 0 H0427: 1 and H0328:	AR052: 7, AR096: 6, AR089: 4, AR060: 4, AR033: 3, AR104: 2, AR033: 3, AR104: 2, AR061: 2, AR039: 1 H0251: 5, H0543: 5, H0615: 3, H0519: 3, T0049: 2, H0051: 2, H0553: 2, H0131: 2, S0422: 2, S0426: 2, H0659: 2, L0752: 2, S0026: 2, H0171: 1, H0556: 1, H0686: 1, H0650: 1, S0116: 1, H0671: 1, S0376: 1, S0046: 1, H0599: 1, H0497: 1, H0156: 1, H0599: 1, H0572: 1, H0015: 1, H0328: 1, H0424: 1, H0032: 1, H0673: 1, S0036: 1, H0328: 1, H0640: 1, H0551: 1, H0673: 1, S0036: 1, H0038: 1, H0640: 1, H0551: 1, T0041: 1, S0210: 1,
	1637 Phe-8 to Gly-21.
	1637
	995 - 69
	232
	760494
	HSXFL85
	222

	ζ,	4
	86-105,	127-144
-		
72: 9: 6:	;; ;;	3: 31:
: 1, ., H06' : 1, , L043 : 1,	2, 1, 1, 0, 11, 2022; 11, 80022; 11, 1 and 1 and	AR039: 19, AR053: 9, AR033: 8, AR055: 8, AR096: 7, AR052: 7, AR089: 6, AR060: 6, AR104: 5, AR061: 4 L0740: 8, H0617: 4, L0740: 8, H0617: 4, AR104: 3, H0068: 2, L0803: AR10547: 2, L0747: 2, L0779: 2, H0587: 1, H0581: AR0649: 1, L0774: 1, L0653:
L0517 1660: 1 10696 742: 1 10780 134: 1,	R055: 2, AR033: R060: 2, AR061: R089: 1, AR096: R052: 0, AR104: S0031: 3, H0624: 1, S0051: 1, H0416: 1, S0058: 1, S0028: 1, S0032: 1, S0028: 1, S0032: 1, S0060: 1, S0	AR039: 19, AR053: R033: 8, AR055: R096: 7, AR052: R089: 6, AR060: R104: 5, AR061: 4, 00804: 3, H0068: 2, I, H0547: 2, L0749: 2, H0547: 1, H0547: 1
77: 1, 1 28: 1, 1 1, LO 16: 1, 1 1, SO 1, SO 10422:	2, 4 1, 2, 4 1, 0, 4 1, 0, 4 1, 3, H 1, 50, 1 1, 50, 1 1, 50, 4 1, 5	19,4 18,4 19,4
1, L0807: 1, L0517: 1, H0520: 1, H0660: 1, H0672: 1, S0328: 1, H0696: 1, L0741: 1, L0742: 1, L0439: 1, L0756: 1, L0780: 1, L0731: 1, S0434: 1, S0196: 1 and H0422: 1.	AR055: 2, AR033: 2, AR060: 2, AR061: 1, AR089: 1, AR096: 1, AR052: 0, AR053: 0, AR039: 0, AR104: 0 S0031: 3, H0624: 1, S6026: 1, S0278: 1, S0222: 1, S0051: 1, H0416: 1, H0644: 1, S0052: 1, S0053: 1, S0028: 1, S0032: 1 and S0260: 1.	AR039: 19, AR053: 9, AR033: 8, AR055: 8, AR096: 7, AR052: 7, AR089: 6, AR060: 6, AR104: 5, AR061: 4 L0740: 8, H0617: 4, L0804: 3, H0068: 2, L0803: 2, H0547: 2, L0747: 2, L0779: 2, H0587: 1, H0581: 1, S0003: 1, H0264: 1, L0649: 1, L0774: 1, L0653:
		Ser-36 Lys-5 Asn-8
		Trp-30 to Ser-36, Lys-54 to Lys-59, Thr-84 to Asn-89.
	m	9 Trp Lys Thr
	1638	1639
	114 - 446	113 - 550
	233	234
	HNGDQ71 760510	760822
	DQ71	нтолт28
	HNG	НТО
	223	224

Γ				-														_										
	91-109, 115-131			-						. <u>.</u>																		
						_			··																			_
162: 1.	v, v,	ς,	4,	0	, S0116:	3,	, S0282:	2,	T0767:	2,	H0657:	1,	H0340:	1,	, H0574:	1,	T0074:	1,	H0530:	1,	, H0059:	1,	L0520:	1,	L0655:	1,	L0664:	1,
and LO	9, AR060: 5, AR052:	5, AR096:	, AR053:	, AR039:	S0436: 5	3, L0809:	H0423: 3	2, H0083:	L0763: 2,	2, S0406:	30114: 1,	1, S0358:	30360: 1,	, H0619:	H0333: 1	1, T0109:	L0021: 1,	1, S0474:	H0327: 1,	1, H0553	H0708: 1	, S0438:	30422: 1,	l, L0761:	.0774: 1,	, L0526:	.0666: 1,	l, H0518
1, L0655: 1 and L0362: 1	AR061: 9 AR033: 5		AR104: 5	AR089: 3, AR039: 0	L0777: 5,	3, L0805: 3, L0809: 3	H0696: 3, H0423: 3, S0282:	2, S0354: 2, H0083: 2,	H0316: 2, L0763: 2, L0767:	2, L0776: 2, S0406: 2,	L0779: 2, S0114: 1, H0657:	, H0656:	S0444: 1, S0360: 1, H0340:	1, S0046: 1, H0619: 1,	H0455: 1, H0333: 1, H0574:	1, H0559: 1, T0109: 1,	[0156: 1,]	1, H0318: 1, S0474: 1,	S0049: 1, H0327: 1, H0530:	, H0615: 1, H0553: 1	H0673: 1, H0708: 1, H0059:	, L0065: 1, S0438: 1	10207: 1,	1, L0769: 1, L0761: 1,	.0521: 1, L0774: 1, L0655:	l, L0659: 1, L0526: 1	.0793: 1, L0666: 1, L0664:	I, H0659: 1, H0518: 1,
			<u> </u>	<u> </u>		<u>e</u>	<u> </u>	-21	<u>;44</u>	2	<u> </u>		<u>S</u>	<u>—</u>	<u>; 11</u>	<u> </u>	<u>i4i</u>		<u>S</u>	_	نكز.	<u>~</u>	<u>;11;</u>					
	Gly-8 to Ser-14.																											
	1640		-																					••				
	532 - 924																											
	235																									·		
	068092																											
	HSDZF13																	-										
	225																											

		
	87-103	64-82
)748:)362:	9, 1, 1, 438: 212: 0042: 0783:	
S0176: 1, H0478: 1, L0748: 1, L0750: 1, L0755: 1, L0731: 1, L0608: 1, L0362: 1, S0026: 1 and S0242: 1.	AR053: 21, AR052: 19, AR096: 14, AR055: 13, AR089: 13, AR033: 11, AR060: 9, AR061: 8, AR104: 7, AR039: 3 L0766: 7, L0439: 7, L0752: 4, L0731: 4, L0438: 3, L0748: 2, L0753: 2, S0276: 2, S0430: 1, S0212: 1, S0358: 1, H0637: 1, S0214: 1, H0637: 1, S0214: 1, H0634: 1, H0272: 1, H0100: 1, H0625: 1, H0130: 1, L0773: 1, L0783: 1, L0791: 1, H0666: 1, S3012: 1, L0780: 1 and H0542: 1.	AR061: 5, AR053: 3, AR055: 1, AR052: 1, AR033: 1, AR060: 1, AR089: 1, AR096: 0, AR039: 0, AR104: 0 S0114: 1, H0549: 1 and 10144: 1.
S0176: 1, 1, L0750: L0731: 1, 1, S0026:	AR053: 2 AR086: 1 AR089: 1 AR104: L0752: 4, 3, L0748: S0276: 2, 1, S0358: S0222: 1, 1, L0040: S0214: 1, 1, L0040: S0214: 1, 1, L0791: S3012: 1, H0542: 1.	AR061: AR055: AR033: AR089; AR039: S0114: J
	Ala-14 to Arg-19, Val-23 to Pro-38, Ser-44 to Gln-53, Pro-69 to Thr-80.	Val-24 to Gly-35, Gly-48 to Ser-59, Ser-123 to Arg-134.
	1641	1642
	47 - 919	105 - 506
	236	237
	761762	761860
	нтовнз9	HE9RP73
	226	227

	T C 17 USU1/10430
111-128, 89-105, 2- 18	37-57
	136550, 203310, 26920, 602772
	6q14
AR055: 10, AR060: 8, AR052: 7, AR061: 7, AR089: 6, AR053: 5, AR089: 5, AR033: 5, AR104: 4, AR039: 4 L0748: 7, L0439: 4, S0410: 3, L0438: 3, L0756: 3, H0252: 2, L0803: 2, L0666: 2, L0754: 2, H0657: 1, S0360: 1, H0431: 1, H0333: 1, H0014: 1, H0328: 1, L0764: 1, L0662: 1, L0794: 1, L0766: 1, L0774: 1, L0653: 1, L0659: 1, L0790: 1, L0352: 1, H0519: 1, L0747: 1, L0749: 1, L0750: 1, L0777: 1, S0192: 1, H0543: 1 and H0423: 1.	AR039: 2, AR033: 1, AR089: 1, AR096: 1, AR055: 1, AR060: 0, AR061: 0, AR053: 0 L0759: 6, L0766: 5, H0052: 4, L0770: 4, L0439: 4, L0740: 4, L0747: 4, H0657: 3, S0358: 3, S0003: 3, L0769: 3, L0754: 3, S0376: 2, H0590: 2, H0040:
Leu-32 to Asn-32, Leu-34 to Pro-39, Glu-80 to Ser-86.	Leu-60 to Asp-68, Ile-75 to Val-82.
. 1643	1644
78 - 692	80 - 436
238	239
762023	764498
228 HSXDG07	HDPHG57
228	229

					-																								
																												-	
2, H0616: 2, L0776: 2,	L0665: 2, H0658: 2, H0521:	2, H0522: 2, L0756: 2,	L0755: 2, L0758: 2, H0445:	2, S0242: 2, H0686: 1,	H0717: 1, S6024: 1, S0116:	1, S0282: 1, H0663: 1,	S0360: 1, H0393: 1, S6026:	1, H0351: 1, H0431: 1,	H0438: 1, H0607: 1, H0642	1, H0632: 1, H0486: 1,	L0021: 1, H0575: 1, H0581:	1, H0597: 1, H0014: 1,	H0071: 1, H0266: 1, H0188:	1, H0622: 1, H0166: 1,	H0169: 1, H0090: 1, H0509	1, S0142: 1, H0695: 1,	H0529: 1, L0369: 1, L0763:	1, L0772: 1, L0794: 1,	L0649: 1, L0803: 1, L0804:	1, L0775: 1, L0805: 1,	L0653: 1, L0809: 1, L0666:	1, L0663: 1, H0144: 1,	L0565: 1, H0547: 1, S0126:	1, S0328: 1, H0539: 1,	S0152: 1, H0555: 1, H0436	1, S3014: 1, L0750: 1,	L0752: 1, L0757: 1, L0591:	1, L0592: 1, L0599: 1,	S0196: 1, H0543: 1, H0422:
							,	-										-											
																								-					

	126-142	182-199,
1 and H0506: 1.	AR096: 1, AR055: 1, AR033: 1, AR089: 1, AR060: 1, AR061: 0, AR052: 0, AR039: 0, AR053: 0, AR104: 0 L0748: 10, L0805: 5, L0750: 3, L0777: 3, H0616: 2, S0422: 2, L0777: 3, H0616: 2, S0422: 2, L0777: 3, H0616: 2, L0779: 1, H0411: 1, H0431: 1, H0042: 1, H0596: 1, H0597: 1, H0050: 1, H0620: 1, H0177: 1, H0050: 1, H0173: 1, H0051: 1, L0779: 1, L0657: 1, L0779: 1, L0438: 1, L0758: 1, L0758: 1, L0759:	AR096: 18, AR053: 16,
		Asp-3 to Arg-8,
	1645	1646
	1220 - 267	- 89
	240	241
	765442	766074
	HGBAD15	HOEEP07
	230	231

					
32-48				· · · · · · · · · · · · · · · · · · ·	
AR052: 13, AR060: 13, AR104: 12, AR061: 12, AR089: 10, AR055: 9, AR033: 8, AR039: 7 L0748: 11, L0766: 6,	L0439: 6, L0758: 6, L0757: 5, L0794: 4, L0756: 4, L0755: 4, L0805: 3, L0776: 3, S0212: 2, S0010: 2,	2, L0771: 2, S0003: 2, L0143: 2, L0770: 2, L0769: 2, L0803: 2, S0126: 2, L0740: 2, L0759: 2, L0591: 2, L0789: 3, H0687: 1, H068: 3, H0688: 1, H0687: 1, H0687: 1, H0688: 1, H068	LUGUS: 2, HUGSS: 1, HUGS 7: 1, H0656: 1, H0341: 1, H0638: 1, S0358: 1, S0360: 1, S0046: 1, S0222: 1, H0497: 1, H0486: 1, T0109:	1, S0474: 1, H0581: 1, H0544: 1, H0009: 1, H0051: 1, H0594: 1, H0032: 1, H0674: 1, H0124: 1, H0038: 1, H0616: 1, H0551: 1,	H0488: 1, L0351: 1, H0560: 1, S0150: 1, S0422: 1, L0763: 1, L0761: 1, L0662: 1, L0788: 1, L0788: 1, L0789: 1, L0666: 1, L0665: 1, H0547: 1, H0658: 1, H0648: 1, S0378:
Gly-22 to Tyr-30, AI Gly-117 to Val-123, AI Glu-256 to Glu-271. AI AI	<u>., 3 E. 5. E.</u>			<u>- 出 - </u> 出 <u>- ;</u>	H C H
1405					,
			· · · · · · · · · · · · · · · · · · ·		

·	102-118	55-77, 75- 91	100-120
			188826, 250100, 250800, 250800
			22q13.2- q13.31
1, H0522: 1, S0146: 1, L0747: 1, L0750: 1, L0752: 1, L0731: 1, H0445: 1, L0588: 1, S0026: 1, S0192: 1, S0276: 1 and H0008: 1.	AR096: 2, AR055: 1, AR089: 1, AR060: 1, AR061: 0, AR052: 0, AR053: 0, AR039: 0, AR033: 0, AR104: 0 H0265: 2, L0766: 2, H0656: 1, H0341: 1, H0581: 1, H0634: 1 and S0194: 1.	AR089: 11, AR096: 11, AR060: 7, AR052: 4, AR053: 3, AR033: 3, AR104: 1, AR039: 0 H0024: 3, H0622: 3, H0265: 1, S0358: 1, H0486: 1, H0150: 1, H0050: 1, S0316: 1, H0100: 1, H0144: 1, S0328: 1 and L0743: 1.	AR055: 11, AR053: 6, AR060: 6, AR096: 6, AR033: 6, AR061: 6, AR052: 4, AR104: 4, AR089: 4, AR039: 3 H0424: 16, S0380: 13,
	Met-1 to Arg-6.	Ser-42 to Arg-47, Thr-115 to Ser-127, Ser-130 to Trp-136.	Asp-9 to Ile-22, Ser-64 to Leu-69, Thr-91 to Ser-100, Lys-162 to Gln-172.
	1647	1648	1649
	19 - 378	905 -	299 - 832
	242	243	244
	766558	298992	767356
	HFIHTS0	HANGD38	234 HPMGQ75 767356
	232	233	234

	· · · · · · · · · · · · · · · · · · ·	
		56-72
84: 666: 683:	32:	375: 427: 78:
L0659: 1, 526: 1, L0384: L0541: 1, 7793: 1, L0666: L0665: 1, 0547: 1, H0683 H0539: 1,	H0627: 1, 027: 1, S00 L0786: 1, 7753: 1, H02 L0592: 1, I L0603: 1.	AR053: 51 AR089: 39 AR089: 34 AR060: 23 AR060: 23 AR059: 17 , L0599: 44 10024: 13, 10123: 9, 7750: 8, HO; L0653: 5, 10653: 5, 10653: 5, 10653: 2, 10653: 2, 10653: 2, 10653: 1, 10776: 4, HO HO208: 2, 10653: 1, 10776: 4, HO
1, L0656: 1, L0659: 1, L0540: 1, L0526: 1, L0384: 1, L0544: 1, L0541: 1, L0789: 1, L0793: 1, L0666: 1, L0664: 1, L0665: 1, H0726: 1, H0547: 1, H0683: 1, H0651: 1, H0539: 1, H0518: 1, S0350: 1, H0555:	1, H0576: 1, H0627: 1, S3014: 1, S0027: 1, S0032: 1, L0756: 1, L0786: 1, L0777: 1, L0753: 1, H0445: 1, L0591: 1, L0592: 1, L0608: 1 and L0603: 1.	AR052: 56, AR053: 51, AR096: 43, AR089: 39, AR055: 39, AR033: 34, AR061: 34, AR060: 23, AR104: 21, AR039: 17 H0575: 138, L0599: 44, H0642: 13, H0024: 13, H0647: 9, L0750: 8, H0375: 5, L0806: 5, L0653: 5, H0649: 4, L0776: 4, H0427: 3, H0646: 3, H0208: 2, H0050: 2, T0003: 2, L0600: 2, H0586: 1, H0318: 1, H0059: 1, S0472: 1, L0378: 1, S0296: 1, H0593: 1,
		Tyr-15 to Cys-22.
		1650
		285 - 695
		245
		767674
		нвли66
		235

_		
	32-55	44-92, 1- 24, 76-92, 41-57
		·
H0539: 1 and L0589: 1.	AR033: 8, AR055: 7, AR052: 5, AR053: 4, AR061: 4, AR060: 4, AR061: 4, AR060: 3, AR104: 3, AR096: 3, AR104: 3, AR096: 3, AR104: 3, L0758: 5, H0620: 3, L0766: 3, 20002: 2, L0748: 2, L0439: 2, L0791: 2, L0747: 2, L0601: 2, H0556: 1, S0282: 1, H0125: 1, T0114: 1, H0549: 1, H0550: 1, S0202: 1, H0622: 1, H0135: 1, H0629: 1, L0769: 1, L076: 1, L0776: 1, L0776: 1, L0783: 1, L0776: 1, L0783: 1, L0543: 1, L076: 1, L0757: 1, L0543: 1, L076: 1, L0757: 1, L0757: 1, L0757: 1, L0757: 1, L0757: 1, L0757: 1, S0260: 1, L0596: 1 and L0361: 1.	AR039: 2, AR096: 2, AR055: 2, AR104: 1, AR033: 1, AR061: 1, AR089: 0, AR053: 0,
	Lys-17 to Cys-29, Thr-69 to Cys-79, Arg-92 to Gly-99.	
	1651	1652
	1022 - 672	26 - 361
	246	247
	768346	768776
	HEGBB78	HAJBC01
	236	237

	-																											9450
	119-137																											
	118425,	118425,	118425,	142335,	152427,	163729,	176450,	180105,	190605,	276000,	276000,	600510,	600725						•			2001 - 11 - 12 - 12 - 12 - 12 - 12 - 12 -						
	7q35-q36																											
AR060: 0, AR052: 0 H0561: 1		AR033: 6, AR061: 5,		AR089: 4, AR052: 3,	AR039: 3, AR053: 3	L0731: 17, L0439: 9,	H0056: 8, L0438: 6, L0759:	6, L0157: 4, H0644: 4,	S0010: 3, L0774: 3, L0747:	3, S0346: 2, H0309: 2,	S0003: 2, S0002: 2, L0646:	2, L0803: 2, L0804: 2,	H0539: 2, S0406: 2, L0748:	2, L0754: 2, L0745: 2,	L0779: 2, L0777: 2, L0780:	2, L0752: 2, H0556: 1,	F0049: 1, H0580: 1, S0045:	1, S0300: 1, H0411: 1,	S0222: 1, H0391: 1, H0333:	l, S0474: 1, L0109: 1,	H0196: 1, H0596: 1, H0050:	l, L0471: 1, H0014: 1,	H0373: 1, H0020: 1, S0051:	l, H0687: 1, L0483: 1,	H0553: 1, H0674: 1, H0163:	1, H0038: 1, H0059: 1,	H0625: 1, H0561: 1, S0144:	1, H0538: 1, S0426: 1,
	Gly-140 to Glu-149.	**	7	7	7		.—		<u> </u>		<u> </u>								<u>.91</u>		<u> </u>		<u> </u>		. Н		<u></u>	
	1653																	•				·		•				
<u></u>	25 - 471																											
	248										-													_				
	769003																											
	HHGCP75	_																-										
	238																											

	252-269, 219-235, 121-137
, 10519: , .0750: I,	12, 11, 11, 6, 6, 7, 7, 10039: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
L0770: 1, L0769: 1, L0764: 1, L0766: 1, L0809: 1, L0791: 1, L0792: 1, H0519: 1, H0521: 1, S0028: 1, L0751: 1, L0749: 1, L0750: 1, L0755: 1, H0668: 1, H0136: 1, H0423: 1 and H0422: 1.	AR055: 20, AR033: 12, AR053: 11, AR052: 11, AR060: 10, AR089: 10, AR061: 9, AR096: 6, AR104: 3, AR039: 3 L0766: 11, L0769: 3, L0761: 3, L0655: 3, L0777: 3, L0780: 3, H0543: 3, H0556: 2, S0476: 2, H0039: 2, L0794: 2, L0804: 2, L0805: 2, L0787: 2, L0747: 2, L0362: 2, S0026: 2, H0542: 1, H0580: 1, S0360: 1, H0580: 1, H0634: 1, H0538: 1, L0483: 1, L0646: 1, L0771: 1, L5574: 1, L0388: 1, L0653: 1, L0606: 1, L0367: 1, L0789: 1, H0144: 1, H0436: 1, L0749: 1 and S0194: 1.
L0770: 1, 1, L0766: L0791: 1, 1, H0521: L0751: 1, 1, L0755: H0136: 1, H0422: 1.	AR055: 2 AR060: 1 AR060: 1 AR104: 3 L0766: 1 L0761: 3, 3, L0780: 4 L0805: 2, L0805: 2, L0805: 2, 1, S0360: S0132: 1, 1, L0646: L5574: 1, 1, L0696: L0789: 1, 1, L0699: 1, 1, L0699: 1, 1, L0699: 1, 1, L0699: 1,
	Pro-17 to Trp-26, Pro-76 to Arg-81, Asp-99 to Gly-106, Pro-148 to His-157, Glu-178 to Glu-185, Leu-195 to Pro-201.
	1654
	24 - 1031
	249
	771350
	HAID095
	239

W U 01/90304	FC1/US01/10450
132-150, 78-94	36-65
124080, 202010, 202010, 214400, 602476,	-
8421	
AR096: 3, AR061: 2, AR053: 2, AR060: 1, AR053: 1, AR052: 1, AR055: 1, AR055: 1, AR104: 0 AR104: 0 S0414: 5, L0663: 4, L0777: 4, L0803: 3, L0744: 3, L0777: 4, L0803: 3, L0744: 3, L0751: 2, L0743: 2, L0751: 2, L0751: 2, L0758: 2, L0758: 2, L0758: 2, L0758: 2, L0756: 1, H0650: 1, H0663: 1, H0650: 1, H0663: 1, H06412: 1, H0623: 1, H0659: 1, L0764: 1, L0766: 1, L0805: 1, L0659: 1, L0664: 1, L0659: 1, L0669: 1, H0435: 1, H0659: 1, H0650: 1, H0659: 1, H0650: 1, H0651: 1, H0659: 1, H0651: 1, H0652: 1, L0764: 1.	AR096: 17, AR055: 9, AR060: 8, AR039: 7, AR061: 6, AR033: 6, AR052: 6, AR053: 5, AR089: 5, AR104: 4 L0766: 3, S0358: 2, S0278:
Lys-20 to Tyr-27, Tyr-35 to Ser-49.	Met-1 to Gly-16, Ser-32 to Lys-38, Ser-64 to Lys-84.
1655	1656
19 - 759	79 - 432
250	251
771648	771900
HE8UD19	HMAIT58
240	241

·	402-418	71-89, 19-	28-58
·			
2, L0775: 2, L0756: 2, H0650: 1, H0656: 1, H0402: 1, H0013: 1, S0049: 1, H0644: 1, H0652: 1, S0142: 1, S0002: 1, L0770: 1, L0768: 1, L0649: 1, L0784: 1, L0776: 1, H0521: 1, H0522: 1 and H0555: 1.	AR055: 1, AR052: 1, AR053: 1, AR061: 1, AR089: 1, AR033: 1, AR104: 1, AR060: 1, AR096: 0, AR039: 0 L0439: 4, H0013: 2, H0497: 1, T0010: 1, T0041: 1, H0144: 1 and L0438: 1.	AR096: 8, AR089: 6, AR052: 5, AR053: 5, AR039: 4, AR033: 3, AR060: 2, AR104: 2, AR055: 2, AR061: 1 L0750: 4, H0265: 3, L0794: 3, L0731: 3, H0635: 2, H0494: 2, L0766: 2, S0116: 1, H0052: 1, H0264: 1, S0002: 1, L0769: 1, L0764: 1, L0768: 1, H0144: 1, L0608: 1 and L0601: 1.	
			Leu-19 to Asn-29,
	1657	1658	1659
	104 -	112 - 423	983 -
	252	253	254
	772217	772639	772840
	HDAAE77	HKAOJ07	HDTFC73
	242	243	244

WO 01/90304	FC1/0501/10450
-	44-60, 129-145
AR096: AR055: AR061: AR060: L0439: S0007: 2 2, L0411 H0638: 1 1, L0021 T0010: 1 1, L0351 L0804: 1 1, S0216	AR096: 2, AR089: 2, AR104: 1, AR060: 1, AR052: 1, AR033: 0, AR039: 0, AR061: 0 S0476: 11, H0556: 10, H0265: 4, H0635: 4, H0657: 2, H0638: 2, S0132: 2, H0036: 2, L0601: 2, H0423: 2, H0713: 1, S0134: 1, S0298: 1, H0486: 1, H0069: 1, H0575: 1, T0082: 1, H0581: 1, L0471: 1, H0321: 1, H0591: 1, H0560: 1, H0641: 1, L0506: 1, L0775: 1, L0657: 1, H0435: 1, H0518: 1, H0521: 1, S0406: 1, L0749: 1 and H0543: 1.
Glu-96 to Lys-101.	Pro-13 to Ser-18.
1303	74 - 538 1660
 (255 74.
	773040
	HDTF132
	245

WU		/90.																											450
12																													
48-64, 72-	,																												1
8	88																												-
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5,	35,	33,	21,	19		07.7	•	035		106	•	07,70		90	٠	017	•	105	•	403	•	105	•	9	•	556		949	
33	33.	6	::	<u> 겪</u>	6,	, T	l: 3	2, S	7:2	2, I	27	., L	 2	, H	5: 1	l, S	3: 1	1, F	3: 1	1, F	5: 1	1, F	3: 1	1, F	0:1	J,	<u></u>	Ţ,	
18	38, AR053: 35,	R05	806	R10	751	2.	19/	7.	5 4	31:	777	9	74	8	329	;;	273	37:	325	52:	54	7.)16	12:)56	4:1	\$	<u>&</u>	8
Į₹,	\ <u>\</u>	\mathcal{A}	Ā	Ą	207	075	7	90	Ξ	<u>2</u>	3	9/0	2	075	H,	990	S.	053	, H(<u>00</u>	H,	5	Ħ,	2	Ħ,	114	3	949	의
8	38	34	26	21.	9,		4.	Η,	∴ 2,	7, H		, ,	.: 	J,		H,		H, H	3: 1	H, H	<u>:</u>	H, H		H, H	1:1	Š.	 1	j	
AR033: 46, AR055: 45,	AR039:	39.	AR096: 26, AR061: 21,	AR060: 21, AR104: 19	H0617: 9, L0751: 6,	.0750: 5, L0752: 5, L0770:	4, L0747: 4, L0761: 3,	.0775: 3, H0657: 2, S0358:	2, S0444: 2, H0457: 2,	H0188: 2, H0181: 2, H0606:	2, L0769: 2, L0772: 2,	.0764: 2, L.0766: 2, L.0774:	2, L0742: 2, L0748: 2,	.0757: 2, L0758: 2, H0624:	, H0685: 1, H0295: 1	S0114: 1, H0661: 1, S0140:	l, H0411: 1, S0278: 1	9.	l, H0013: 1, H0253: 1,	H0318: 1, H0052: 1, H0309:	, H0204: 1, H0545: 1	H0033: 1, H0424: 1, H0598:	, H0135: 1, H0163: 1,	H0616: 1, H0412: 1, H0059:	l, H0494: 1, H0560: 1,	S0440: 1, S0144: 1, L5565:	I, L0373: 1, L0646: 1,	.0768: 1, L0499: 1, L0497:	, L0513: 1, L0783: 1
R 0	R 0	ROS	R 0	ROK	90	375	2	777	S0	018	2	376	2	375	H)11	H	054	HO	031	Ξ	9	H	061	H	<u>¥</u>	2	9/(의
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12	-10																												
	Pro																												
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Gly-5 to Gln-12,	Lys-98 to Pro-106.																												-
													-																
1661																													
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-37																													1
256 47 - 373																													- 1
9								_								_				_									
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347																													
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246 HLQCY70 773347																											•		\exists
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·	61-77	144-160, 99-115
L0384: 1, L0519: 1, L3872: 1, L0368: 1, L0665: 1, S0053: 1, H0144: 1, H0670: 1, H0696: 1, S0406: 1, L0740: 1, L0754: 1, L0780: 1, L0731: 1, L0596: 1, S0026: 1, H0543: 1, H0677: 1 and H0352: 1.	AR055: 5, AR052: 3, AR061: 3, AR033: 3, AR060: 2, AR089: 2, AR039: 2, AR104: 2, AR053: 1, AR096: 1 S0045: 1, S0222: 1, H0250: 1, H0617: 1 and S0028: 1.	AR055: 7, AR104: 10, AR055: 7, AR060: 5, AR061: 5, AR052: 5, AR096: 4, AR089: 4, AR053: 3, AR039: 2 S0010: 4, S0222: 3, H0455: 2, L0803: 2, L0439: 2, L0745: 2, S0282: 1, S0400: 1, H0722: 1, H0456: 1, H0441: 1, S0346: 1, H0714: 1, H0509: 1, L0769: 1, L0793: 1, L0438: 1,
	Lys-31 to Lys-39, Gln-41 to Lys-46, Pro-79 to Ala-85, Glu-95 to Leu-100.	THINNE
	1662	1663
	2 - 301	649 - 41
	257	258
	773740	774276
<u>.</u>	HELDG78	HAGEK19
	247	248

	114-130, 147-163									60-78, 17-	33								90-116,	51-70, 79-	95, 21-37			44-65, 92-	112, 21-
						-										·									
L0756: 1, S0434: 1 and S0106: 1.	AR055: 11, AR033: 9, AR060: 6, AR104: 6,	AR096: 6, AR061: 5,	AR089: 4, AR053: 4,	AR052: 4, AR039: 3	L0740: 2, S0222: 1,	T0082: 1, T0110: 1, T0010:	1, L0483: 1, L0763: 1,	L0639: 1, L0747: 1, L0777:	1, L0758: 1 and L0599: 1.	AR052: 8, AR053: 7,	AR033: 3, AR055: 3,	AR096: 3, AR089: 2,	AR061: 2, AR060: 2,	AR104: 1, AR039: 0	L0777: 5, L0439: 2,	L0596: 2, T0004: 1, L0658:	1, H0518: 1, H0521: 1,	L0731: 1 and S0106: 1.	AR055: 17, AR033: 13,		AR089: 10, AR053: 10,	AR061: 9, AR060: 8,	AR096: 7, AR104: 7	 AR055: 2, AR089: 1,	AR104: 1, AR060: 1,
	Asp-20 to Leu-26, Gln-55 to Thr-60,	Asn-74 to Asn-86.									•								Met-1 to Arg-7.					1667 Gln-11 to Arg-21.	
	1664									1665									1666					1667	
	291 - 854									465 -	764								273 -	734		,		152 -	592
	259									260									261					262	
	774569									774739									775247					775419	
	H2CBA34									250 HDPTC79 774739									HTHBY73					HE8DL19	
	249									250									251					252	

1	
37, 124- 140	102-131
	.66: 54: 775: 62: 713: 515: 75:
AR096: 0, AR061: 0, AR033: 0, AR053: 0, AR052: 0 H0013: 1, S0214: 1, H0615: 1 and L0544: 1.	AR055: 7, AR052: 5, AR096: 5, AR060: 4, AR053: 3, AR033: 3, AR089: 3, AR104: 3, AR061: 3, AR039: 2 L0766: 8, L0777: 7, L0794: 5, L0770: 4, H0266: 3, L0803: 3, L0776: 3, H0144: 3, L0740: 3, L0754: 3, L0750: 3, S0222: 2, S0414: 2, H0013: 2, H0575: 2, H0590: 2, L0764: 2, L0769: 2, L0764: 2, L0769: 2, L0769: 2, L0769: 2, L0789: 2, H0696: 2, L0439: 2, L0765: 1, H0641: 1, H0696: 1, H0641: 1, H0697: 1, L0041: 1, H0697: 1, L0041: 1, H0698: 1, H0560: 1, H0641: 1, H0598: 1, H0561: 1, H0412: 1, H0560: 1, H0641: 1, L0796: 1, L0761: 1,
AR096: AR033: AR039: H0013: 1	AR055: AR096: AR089: AR089: AR061: L0766: 8 L0794: 5, 3, L0803: H0144: 3, 3, L0750: S0414: 2, 2, H0590: L0769: 2, 2, L0809: H0696: 2, 2, S0026: H0696: 2, 1, S0045: H0697: 1, 1, H0053: 1, 1, H0053: 1, 1, H0083: 1, 1, L0796: L0771: 1,
E	Leu-12 to Thr-19, Arg-25 to Glu-39, Glu-41 to Cys-48, Ser-65 to Ser-71, Pro-84 to Gly-89, Ser-97 to Arg-103.
	1668
	31 - 423
	763
	775455
	HMEGE46
1 1.	253

·	349-366, 272-288, 380-396
1, LO788: 1, H0522: 1, S0031: 1, and	6, 4, 4, 3, 2 111, 10759: 4, H0083: 2, L0770: 2, L0770: 2, L0749: 2, L0749:
1, L0375: 1, L0806: 1, L0805: 1, L0659: 1, L0788: 1, L0666: 1, H0520: 1, H0660: 1, H0521: 1, H0522: 1, S0406: 1, H0555: 1, S0028: 1, L0747: 1, S0031: 1, L0608: 1, L0593: 1, H0668: 1, S0242: 1 and H0423: 1.	AR055: 6, AR052: 6, AR053: 4, AR060: 4, AR089: 4, AR104: 2, AR039: 2 L0748: 11, L0758: 11, L0594: 6, L0439: 5, L0759: 5, H0556: 4, L0769: 4, S0442: 3, H0036: 3, H0083: 3, L0756: 3, L0756: 3, L0756: 3, L0756: 3, L0756: 3, L0756: 3, L0769: 2, H0038: 2, H0551: 2, L0564: 2, L0771: 2, L0569: 2, L0649: 2, L0539: 2, L0760: 2, L0740: 2, L0747: 2, L0740: 2, L0747: 2, L0740: 2, L0757: 2, L0759: 2, L0758: 2, L0559: 2, L0559
1, L0375 L0805: 1 1, L0666 H0660: 1 1, S0406 S0028: 1 1, L0608 H0668: 1 H0423: 1	
	Val-29 to Asp-34, Gln-78 to Gln-86, Val-94 to Leu-100, Glu-112 to Leu-117, Gln-119 to Ile-133, Glu-152 to Ala-157, Thr-159 to Gln-168, Lys-209 to Glu-218, Thr-225 to Ser-231, Trp-410 to Trp-415, Ala-505 to Ser-510.
	1669
·	1657
	264
	778081
	HTEIA85
	254

		73-97,
	·	
212: 580: 222: 222: 0045: 0673: 369: 388:	014:	5,
386:1, 501, 1, 100, 1, 1, 100, 1, 1, 100, 1, 1, 100, 1, 1, 10, 10	27. 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	55: 10
2, H02 1, H02 1, H02 1, S03 203 203 1, H03 1, H04 1, H04 1, S03 1, T00 1, T00 1, T00 1, T00 1, T00 1, T00 1, T00 1, T07 1, L07 1, L07	1, LO790 1, HO1 1, HO5 1, HO5 HO436 HO436 HO543	6, AR(
2, L0595: 2, H0686: 1, S0040: 1, H0295: 1, S0212: 1, H0255: 1, H0661: 1, S0444: 1, S0360: 1, H0580: 1, H0729: 1, S0046: 1, L0717: 1, S0278: 1, S0222: 1, H0057: 1, H0054: 1, H0054: 1, H0054: 1, H0054: 1, H0054: 1, H0059: 1, H0674: 1, H0169: 1, H0060: 1, S0440: 1, H0509: 1, S036: 1, S0440: 1, H0509: 1, S0444: 1, S0382: 1, L0764: 1, L0538: 1, L0768: 1, L076	1, LO77 1, LO527 1, L5623: 1, L0790: 1, L0663: 1, L0648: 1, H0144: 1, L0438: 1, H0519: 1, H0648: 1, H0521: 1, H0522: 1, S0013: 1, H0436: 1, S3014: 1, S0027: 1, L0751: 1, L0779: 1, H0543: 1 and L0600: 1.	AR052: 16, AR055: 16,
2, 1 80, 1 1, 1	1, 1 1, 1 1, 1 1, 8 1, 8 1, 8 1, 8 1, 8	AR
		ln-28.
		Ala-18 to Gln-28.
		1670
		270 -
		265
		087
		3 778087
		HSHBF13
		├
		255

108-134, 42-58	52-72, 7- 23 .
AR053: 14, AR033: 12, AR060: 10, AR089: 8, AR096: 7, AR061: 7, AR104: 5, AR039: 4 H0046: 6, L0758: 5, L0794: 3, L0803: 3, L0779: 3, H0052: 2, H0424: 2, H0135: 2, L0809: 2, L0789: 2, H0690: 2, S3014: 2, L0743: 2, L0751: 2, L0731: 2, H0295: 1, S0001: 1, S0282: 1, H0484: 1, H0306: 1, S0360: 1, S0278: 1, S0002: 1, H0457: 1, H0031: 1, H0316: 1, H0038: 1, L0650: 1, L0774: 1, L0655: 1, L0650: 1, L0659: 1, L0664: 1, L0665: 1, H0547: 1, H0435: 1, H0670: 1, S0037: 1, L0748: 1, L0599: 1 and L0601: 1.	AR053: 1, AR060: 1, AR055: 1, AR033: 1, AR061: 0, AR089: 0, AR096: 0, AR052: 0, AR039: 0, AR104: 0 L0758: 13, L0756: 3, L0752: 3, L0438: 2, H0176:
AR053: 14, AR AR060: 10, AI AR060: 10, AI AR096: 7, AR AR104: 5, AR H0046: 6, L07 L0794: 3, L080 3, H0052: 2, H0 H0135: 2, L080 2, H0690: 2, S3 L0743: 2, L075 2, H0690: 1, S0 S0282: 1, H048 1, S0360: 1, S0 S6022: 1, H045 1, L0764: 1, L0 L0650: 1, L077 1, L0658: 1, L0 L0664: 1, L066 1, H0435: 1, H0 S0007: 1, L074 1, H0435: 1, H0 S0037: 1, L074 1, H0435: 1, H0 S0037: 1, L074 1, H0435: 1, H0	AR053: AR055: AR061: AR096: AR039: L0758: 1 L0752: 3,
•	Lys-31 to Thr-39.
	1671
707	539 - 240
·	266
	778291
	256 HLYCQ80
	256

	91-107	103-120
1, H0261: 1, H0309: 1, H0081: 1, H0029: 1, H0038: 1, H0616: 1, H0202: 1, L0369: 1, L0766: 1, L0774: 1, L0776: 1, L0635: 1, L0809: 1, L0791: 1, H0547: 1, H0711: 1, H0690: 1, S0152: 1, H0479: 1, L0743: 1, L0439: 1, L0750: 1, L0777: 1, L0755: 1, H0445: 1 and L0588: 1.	AR055: 13, AR060: 9, AR052: 9, AR061: 8, AR053: 8, AR033: 5, AR089: 4, AR096: 3, AR104: 2, AR096: 3, L0761: 3, L0439: 3, L0747: 3, L0766: 2, H0659: 2, L0779: 2, L0777: 2, H0170: 1, S0360: 1, H0550: 1, H0023: 1, H0018: 1, H0641: 1, L0763: 1, L0769: 1, L0764: 1, L0803: 1, L0774: 1, L0655: 1, L0666:	AR052: 285, AR089: 170, AR096: 161, AR053: 143, AR060: 83, AR104: 64, AR033: 49, AR039: 43,
	1672 Met-1 to Gln-8, Leu-17 to Leu-29, Gln-109 to Thr-115.	Glu-53 to Asp-58, Trp-98 to Lys-103, Leu-131 to Arg-144.
	1672	1673
	162 - 611	52 - 630
	267	268
	778504	779291
	HE2OF81	HTEBB88
	257	258

	18-44, 75-
	121011, 121011, 129500, 253700, 601885, 602221
	13q12
AR061: 42, AR055: 40 L0758: 6, H0616: 3, H0038: 2 and H0618: 1	AR039: 23, AR104: 18, AR039: 23, AR104: 18, AR052: 8, AR056: 10, AR055: 6, AR089: 6, AR060: 5, AR061: 4 L0754: 16, H0617: 8, S0360: 6, H0551: 6, L0748: 6, L0756: 5, L0666: 5, L0751: 5, L0747: 5, S0418: 4, H0553: 4, L0665: 4, H0542: 4, H0558: 3, L0747: 5, S0414: 3, H0264: 3, H0494: 3, S0344: 3, L0769: 3, L0757: 3, L0769: 3, L0757: 3, L0740: 3, L0757: 2, H0559: 2, H0559: 2, H0688: 2, L0770: 2, L0771: 2, L0662: 2, L0653: 2, L0659: 2, L0662: 2, L0659: 2, L0771: 2, L0660: 2, L0659: 2, L0771: 2, L0660: 2, L0673: 2, H0435: 2, H0660: 2, L0588: L0731: 2, L0759: 2, L0588: L05888: L05888: L05888: L05888: L05888: L05888: L05888: L05888:
	Asn-14 to Ser-19, Asp-46 to Phe-51, Glu-101 to Asp-117, Ile-121 to Gly-127.
	1674
	81 - 461
	569
	779607
	HWHGD8 2
	259

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2, H0265	1,	S0110:	1,	S0356:		S0278:	1,	H0632:	1,	H0597:	1,	H0562:	1,	H0428:	1,	H0040:	1,	H0100:	1,	L0598:	I,	L0761:	1,	L0773:	1,	L0651:	1,	L0787:
L0601:	H0583:	0341: 1,	H0662:)420: 1,	S0444:	717: 1,	H0370:	0497: 1,	H0599:	0110: 1,	H0457:	0009: 1,	H0594:	0271: 1,	H0181:	364: 1,	H0063:	0413: 1,	S0448:)131: 1,	L0763:	637: 1,	L0646:	644: 1,	L0649:	375: 1,	L0607:	657: 1,
2, L0599: 2, L0601: 2, H0506: 2 H0352: 2 H0265:	1, H0556: 1, H0583: 1,	H0657: 1, H0341: 1, S0110:	1, H0484: 1, H0662: 1,	02: 1, S(1, S0354: 1, S0444: 1,	30: 1, LC)222: 1,	H0415: 1, H0497: 1, H0632:	1, H0486: 1, H0599: 1,	18: 1, T	0046: 1,	50: 1, H	1, H0014: 1, H0594: 1,	79: 1, H	0424: 1,	L0055: 1, S0364: 1, H0040:	1, H0634: 1, H0063: 1,	H0488: 1, H0413: 1, H0100:	1, H0561: 1, S0448: 1,	40: 1, H(1, H0529: 1, L0763: 1,	39: 1, L(0772: 1,	00: 1, LO	l, L0521: 1, L0649:	.0381: 1, L0375: 1, L0651:	1, L0655: 1, L0607: 1,	77: 1, LC
2, LC	1, H	H06	1, H	H04	1, S(S03(1, S(H04	1, H	H03	1, H	H01	1, H	H01	1, H	100	1, H	H04	1, H	S04	1, H	.90T	1. L	<u> </u>	1, L	<u>103</u>	1, L) []
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	102-119
1, L0663: 1, S0428: 1, H0144: 1, H0593: 1, S0126: 1, H0690: 1, H0670: 1, S0328: 1, S0380: 1, S0350: 1, H0522: 1, S0188: 1, S0027: 1, S0206: 1, L0744: 1, L0439: 1, L0756: 1, L0777: 1, L0755: 1, H0445: 1, H0136: 1, S0042: 1 and L0697: 1.	AR052: 5, AR053: 3, AR089: 2, AR060: 2, AR104: 2, AR061: 1, AR055: 0, AR039: 0 L0439: 7, L0759: 5, H0624: 4, H0170: 4, S0003: 4, L0766: 4, H0657: 3, H0013: 3, L0438: 3, H0068: 2, L0598: 2, L0646: 2, L0794: 2, L0559: 2, L0779: 2, L0666: 2, H0520: 2, L0747: 2, L0588: 2, L0777: 2, L0588: 2, L0592: 2, H0171: 1, H0556: 1, S0376: 1, S0045: 1, S0222: 1, H0586: 1, T0114: 1, H0581: 1, L0471: 1, H0355: 1, S6028: 1, S0214:
	Glu-37 to Asn-44.
	1675
	143 - 628
·	270
	779663
	нWADH6 7
	260

	86-110, 7- 32, 65-82	99-121, 124-140	60-77, 22- 38
0040: 806: 519: 780:	773:		5,
14 4 4 4 4 6 4 4 4 4 4 4	AR052: 3, AR033: 2, AR104: 2, AR089: 2, AR055: 2, AR039: 2, AR096: 2, AR053: 2, AR061: 1, AR060: 1 L0766: 5, H0494: 2, L0755: 2, L0800: 1, L0773: 1 and L0777: 1.	AR052: 3, AR053: 2, AR104: 2, AR089: 1, AR033: 1, AR061: 1, AR060: 1, AR096: 1, AR055: 0, AR039: 0 H0543: 1	AR033: 20, AR104: 16, AR055: 8, AR061: 7, AR060: 5, AR053: 5,
	Asn-3 to Phe-9.	1677 Met-1 to Glu-10.	Pro-89 to Phe-96.
	1676	1677	1678
	530	29 - 457	822 - 502
	271	272	273
	779838	780458	780804
	261 HKADC82	HHESK83	HMIAT16
	261	262	263

	9-29, 120- 136	77-95, 10- 26	80-162, 1-
AR052: 5, AR089: 5, AR096: 4, AR039: 3 S0414: 3, S0036: 3, L0439: 3, H0327: 2, H0051: 2, S6028: 2, S0282: 1, H0406: 1, H0438: 1, S0010: 1, S0038: 1, S0260: 1 and S0412: 1.	AR053: 2, AR096: 1, AR089: 1, AR060: 1, AR104: 1, AR055: 1, AR033: 0, AR039: 0, AR061: 0, AR052: 0 H0164: 1 and S0390: 1.	AR052: 3, AR096: 3, AR053: 2, AR089: 2, AR033: 2, AR089: 1, AR060: 1, AR104: 1, AR055: 1, AR061: 0 L0439: 2, L0747: 2, L0756: 2, H0556: 1, S0116: 1, H033: 1, H0427: 1, H0156: 1, H0652: 1, S0210: 1, L0769: 1, L0646: 1, L0657: 1, L0384: 1, L0543: 1, H0670: 1, H0521: 1, H0478: 1, L0745: 1, L0749: 1, L0757: 1 and L0591: 1.	AR033: 8, AR060: 6,
	1679 Asp-39 to Gln-44.	Pro-37 to Cys-42, Pro-52 to Gly-63.	Ile-35 to Ser-44.
	1679	1680	1681
	149 - 763	29 - 340	24 - 401
	274	275	276
	780819	781376	781623
	HSLJK83	HADFW62	HDTBV64
	264	265	566

42 42 439 445 438 438 438 438 438 438 438 438 438 438
SO SO HO HO HO HO SO
5549.6088454094549444644646464
20.05 20
AR082: 3, AR096: 3, AR082: 2, AR053: 2, AR061: 1, AR104: 1, AR061: 1, AR104: 1, AR065: 0, AR039: 0 L0752: 8, L0766: 6, S0444: 5, L0770: 5, L0439: 5, L0731: 5, S0360: 3, H0031: 3, L0803: 3, S0126: 3, L0755: 3, L0758: 3, S0358: 2, H0056: 2, L0665: 2, L0665: 2, H0050: 2, H0056: 2, L0666: 2, L0665: 2, H0050: 1, H0519: 2, S0330: 2, H0521: 2, L0747: 2, H0170: 1, H0716: 1, H0740: 1, S0354: 1, H0440: 1, S0354: 1, H0431: 1, H0574: 1, H0331: 1, H0574: 1, H0581: 1, H0374: 1, H0581: 1, H0374: 1, H0581: 1, H0374: 1, H0581: 1, H0374: 1, S0214: 1, H0428: 1, H0622: 1, H0428: 1, H0622: 1, H0553: 1, H0163: 1, H0087: 1, H0560: 1, S0438: 1, H0087:
% % 1 % 1 % 1 % 1 % 1 % 1 % 1 % 1 m 1 m
AR089: AR052: AR052: L0752: S0444: 5 5, L073: 3, L075: 1, H0031: 1, H001: 1, H033: 1, H033: 1, H054: 1, H054: 1, H054: 1, H054: 1, H058: 1, H054: 1, H054:
1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1
AAAA MOHENDADADADADADADADADADADADADADADADADADADA

	55-78, 31- 48	207-223
·		
		·
1, S0440: 1, S0426: 1, UNKWN: 1, L0598: 1, L0763: 1, L0769: 1, L0638: 1, L0761: 1, L0641: 1, L0776: 1, L0379: 1, L0657: 1, L0809: 1, L0519: 1, L0791: 1, L0663: 1, H0684: 1, H0672: 1, S0378: 1, H0522: 1, S0404: 1, S0406: 1, S0028: 1, L0750: 1, L0756: 1, L0753: 1, S0031: 1, H0445: 1, H0595: 1, S0436: 1, L0581: 1, L0608: 1, S0011: 1, S0026: 1, S0192: 1, S0196: 1, H0423: 1 and S0424: 1.	AR096: 1, AR052: 1, AR033: 1, AR060: 1, AR089: 1, AR061: 0, AR055: 0, AR053: 0, AR104: 0 H0009: 2, H0583: 1, S0045: 1 and S0250: 1.	AR096: 6, AR053: 6, AR052: 4, AR089: 3, AR060: 2, AR039: 2, AR033: 2, AR055: 2, AR104: 2, AR061: 1 L0740: 8, L0749: 8,
·	Met-1 to Gly-7, Pro-99 to Phe-104.	Glu-46 to Asn-51, Gly-56 to Gly-63.
	1682	1683
	225 - 578	119 - 901
	277	278
	781821	782028
	267 HOHBR65	HRABZ84
	267	268

																		-											
										- 																			
, L0779:	. 3,), L0752:	: 2,	2, L0774:	. 2,	2, L0754:	: 2,	l, H0685:	7: 1,	, S0046:	:1,	I, H0587:	: 1,	1, H0318:	5: 1,	., H0687:	:1,	1, H0641:	: 1,	, L0386:	.1,	, H0519:	5: 1,	l, L0746:	1,	, S0308:	: 1,	, S0192:	
S0040: 4, L0766: 4, L0779:	L0471: 3, H0090	H0040: 3, L0748: 3, L0752:	3, S0358: 2, H0644: 2,	H0616: 2, L0763: 2, L0774:	L0659: 2, L0809	H0144: 2, L0744: 2, L0754:	L0750: 2, L0777	0758: 2, H0686: 1	H0583: 1, H0657	H0662: 1, S0360: 1, S0046:	l, L0717: 1, H0351: 1,	H0549: 1, H0586: 1, H0587:	H0013: 1, S0280	H0156: 1, H0575: 1, H0318:	1, H0231: 1, H0046: 1,	S6028: 1, H0266: 1, H0687:	1, S0003: 1, S0214: 1	H0063: 1, H0264: 1, H0641:	1, S0002: 1, S0426: 1,	.0764: 1, L0662: 1, L0386:	l, L0775: 1, L0654: 1	.0665: 1, L0438: 1, H0519:	H0593: 1, H0365	H0555: 1, L0439: 1, L0746:	L0747: 1, L0756	L0780: 1, L0755: 1, S0308:	l, L0591: 1, L0362: 1	.0366: 1, S0026: 1, S0192:	and H0506: 1.
S	<u>4,</u>	I	<u>3</u>	耳	-Ci	Ī	2,	<u>⊒</u>	<u>, </u>	耳	1,	臣	1,	Ē	1,	<u>x</u>	<u>1</u>	H	1,	ī	1,	Ä	1,	耳	<u></u>	ī	1,	Ä	1
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WO 01/90304	FC1/US01/10450
51-67	45-61
	·
996: 47, 553: 25, 552: 22, 600: 17, 51: 3 87: 1, 87: 1, 11, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	53: 3, 89: 1, 55: 1, 50: 1, 39: 0 39: 0 39: 0 39: 0 39: 0 39: 0 39: 1, 47: 2, 12, H0638: 77: 1, 11, H0625: 54: 1,
AR089: 47, AR096: 47, AR104: 33, AR053: 25, AR039: 23, AR052: 22, AR033: 22, AR060: 17, AR055: 4, AR061: 3 L0803: 2, L0748: 2, H0556: 1, S0134: 1, H0734: 1, S0010: 1, H0687: 1, H0428: 1, H0494: 1, L0662: 1, L0809: 1, L0776: 1, L0809: 1, L0787: 1, S0152: 1, H0522: 1, L0439: 1, L0756: 1, L0752: 1, L0758: 1, L0599: 1, L0601: 1 and H0543: 1.	AR052: 5, AR053: 3, AR096: 2, AR089: 1, AR033: 1, AR055: 1, AR104: 1, AR050: 1, AR061: 1, AR039: 0 L0439: 5, L0770: 4, L0794: 4, L0758: 4, L0665: 3, H0657: 2, S0360: 2, H0039: 2, H0040: 2, H0551: 2, L0803: 2, L0747: 2, L0777: 2, H0423: 2, H0638: 1, S0420: 1, S0007: 1, H0050: 1, H0510: 1, H0594: 1, S0003: 1, H0264: 1,
1684 Met-1 to Pro-6, Thr-18 to Ala-32, Gln-39 to Gly-44. Flight Heritage Street	Met-1 to Arg-7, Pro-9 to Ile-17, Glu-26 to Tyr-38. Ill Ill Ill Ill Ill Ill Ill Ill Ill I
1684	1685
30 - 338	231 - 1040
279	280
782431	783017
HKABD18 782431	HUFAJ06
269	270

	123-142	300-316, 176-192
8: 1, 1, L0766: 4: 1, 1, H0435: 9: 1, 1 and	33: 42, 53: 36, 50: 14, 96: 11, 94: 6	2: 3, 0: 3, 6: 2, 9: 1, 11: 1 9: 5, 4, \$0422: 11: 3, 3, L0646: 17: 3, 3, H0423: 0: 2, 2, H0672: 2, H0672:
1, L0598: 1, L0648: 1, L0662: 1, L0768: 1, L0766: 1, L0804: 1, L0774: 1, H0547: 1, H0519: 1, H0435: 1, S0380: 1, L0759: 1, H0445: 1, H0542: 1 and H0506: 1.	AR052: 51, AR033: 42, AR055: 40, AR053: 36, AR089: 30, AR060: 14, AR061: 12, AR096: 11, AR039: 10, AR104: 6	AR033: 3, AR052: 3, AR089: 3, AR060: 3, AR053: 2, AR096: 2, AR055: 1, AR039: 1, AR104: 1, AR061: 1 L0766: 12, H0659: 5, L0749: 5, S0410: 4, S0422: 4, H0650: 3, H0541: 3, H0521: 3, L0748: 3, H0423: 3, H0557: 2, S0280: 2, H0566: 2, H0699: 2, H0040: 2, L0803: 2, L0804: 2, L0666: 2, H0658: 2, H0672: 2, L0756: 2, L0757: 2,
<u></u>	37.	
	1686 His-13 to Gln-20, Gly-27 to Ser-55, Glu-175 to Gly-187.	Leu-26 to Gly-33, Glu-44 to Cys-49, Gln-54 to Ile-62, Glu-75 to Lys-80.
	1686	1687
	77 - 667	1155
	281	282
	783316	783318
	HDQFV46	нмекн64
	271	272

/O 01/90304	_ 51, 5501, 10450
	43-67, 17- 34
	·
5. 2, H0170: 5.56: 1, 2: 1, S0418: 44: 1, 318: 1, 318: 1, 5: 1, H0024: 5: 1, H0625: 47: 1, 74: 1, 11, L0776: 35: 1, 5: 1, L076: 5: 1, L076: 74: 1, 5: 1, L076: 74: 1, 5: 1, L076: 74: 1, 5: 1, L076: 74: 1, 5: 1, L0750: 75: 1, H0670: 96: 1,	55: 8, 55: 7, 52: 6, 60: 5, 61: 4 52: 2, 51: 1, H0253:
L0759: 2, S0424: 2, H0170: 1, H0556: 1, H0662: 1, S0418: 1, S0420: 1, S0444: 1, H0728: 1, S0045: 1, L0717: 1, H0428: 1, H0318: 1, H0596: 1, T0110: 1, H0624: 1, H0596: 1, H0616: 1, H0551: 1, H0660: 1, H0625: 1, L0764: 1, L0520: 1, L0764: 1, L0520: 1, L0764: 1, L0655: 1, L0774: 1, L0655: 1, L0789: 1, L0663: 1, L0665: 1, L0789: 1, L0663: 1, L0655: 1, L0439: 1, L0750: 1, L0777: 1, L0752: 1, L0777: 1, L0752: 1, L0758: 1, L0608: 1, L0777: 1, L0758: 1, L0608: 1, L0758: 1, L0758: 1, L0759: 1, L0758: 1, L0759: 1, L0758:	AR039: 10, AR055: 8, AR033: 7, AR053: 7, AR089: 6, AR052: 6, AR096: 5, AR060: 5, AR104: 5, AR061: 4 H0618: 3, H0052: 2, H0411: 1, H0333: 1, H0253: 1, H0622: 1, H0424: 1,
	Gln-77 to Ala-82, Thr-90 to Asp-100, Leu-108 to Ala-120.
	1688 C
	51 - 413
,	283
	783631
	HTLEE85
	273

	170-186, 120-136	67-89, 91- 107	40-62, 19- 35
	•		
S0378: 1, L0749: 1 and S0436: 1.	AR104: 12, AR096: 11, AR053: 10, AR055: 10, AR052: 9, AR060: 8, AR033: 7, AR089: 7, AR061: 5, AR039: 5 H0038: 5, H0616: 5, L0758: 5, S0003: 3, L0741: 3, S0278: 2, H0156: 2, H0052: 2, S0144: 2, S0344: 2, L0768: 2, S0218: 1, H0484: 1, H0638: 1, S0045: 1, S0046: 1, H0438: 1, H0562: 1, L0769: 1, L0794: 1, S0122: 1 and L0749: 1.	AR055: 8, AR052: 7, AR089: 6, AR060: 6, AR096: 5, AR033: 5, AR104: 5, AR053: 4, AR039: 4, AR061: 4 H0615: 4 and H0556: 1.	AR104: 240, AR061: 184, AR060: 129, AR033: 121, AR089: 99, AR053: 77, AR052: 76, AR055: 67, AR039: 62, AR096: 56 S0136: 8, L0754: 5, L0758: 5, L0768: 3, L0766:
	Gly-10 to Arg-18, Leu-23 to Lys-30, Gly-53 to Pro-60, Asn-72 to Arg-81, Ser-86 to Lys-95, Glu-97 to Asp-105.		Thr-37 to Ser-43, Pro-62 to Asn-67, His-73 to Tyr-82, Pro-94 to Ser-102.
	1689	1690	1691
	73 - 795	29 - 382	1035 - 1340
	284	285	286
	783713	783883	783892
	HCE4Q82	норес95	HCBBA47
	274	275	276

U 01/90304	PC1/USU1/10450
	517-533, 476-492
	223900, 253800, 253800
	9q31.2
3, L0803: 3, L0749: 3, H0506: 2, L0662: 2, L0794: 2, L0804: 2, L0794: 2, L0804: 2, L0747: 2, H0550: 1, L0747: 2, L0755: 2, L0685: 2, H0573: 1, H0580: 1, S0222: 1, H0542: 1, H0560: 1, H0266: 1, H0543: 1, H0579: 1, H0266: 1, H0553: 1, H0579: 1, L0772: 1, L0764: 1, L0667: 1, L0772: 1, L0764: 1, L0667: 1, L0772: 1, L0764: 1, L0665: 1, H0672: 1, H0579: 1, L0746: 1, L0769: 1, L0779: 1, L0770: 1, H0571: 1, L0770: 1, L07	1692 Met-1 to Lys-6, AR052: 26, AR033: 26, Ser-31 to Ala-45, AR053: 18, AR089: 15, Cys-102 to Glu-107, AR060: 9, AR096: 9, Arg-151 to Asp-157, AR055: 8, AR104: 6, Glu-215 to Leu-220, H0266: 4, H0547: 4, Ser-264 to Leu-270, H0521: 3, L0748: 3, S0358:
	577 - 2247
	783939 287
	нѕкеQ61
	777

	32-57
2, L0471: 2, H0373: 2, H0068: 2, H0435: 2, H0435: 2, S0152: 2, L0754: 2, L0603: 2, S0192: 2, H0170: 1, H0657: 1, S0212: 1, H0638: 1, S0354: 1, H0580: 1, S0045: 1, H06431: 1, H0633: 1, T0039: 1, H0040: 1, H0687: 1, S0049: 1, H0687: 1, S0150: 1, H0069: 1, H0649: 1, L0803: 1, S0150: 1, H0652: 1, H0660: 1, H0672: 1, S0050: 1, H0672: 1, S0027: 1, S0028: 1, L0740: 1, L0757: 1, L0755: 1, L0757: 1, L0759: 1, S0026: 1, L0759: 1, L0759: 1, S0026: 1, L0593: 1, L0759: 1, L0593: 1, L0759: 1, S0026: 1, L0593: 1, S0026: 1, L0593: 1, S0026: 1, L0593: 1, S0026: 1, S0194: 1, S0196: 1 and S0194: 1, S0196: 1 and S0424: 1.	AR104: 1, AR033: 1, AR089: 1, AR053: 0, AR096: 0, AR061: 0, AR039: 0, AR052: 0, AR060: 0, AR055: 0
Gly-351 to Gly-358, 2, L0471; 2, H0373; 2, Lys-364 to Asn-371, H0068; 2, H0509; 2, H Ser-374 to Gln-385, 2, H0435; 2, S0152; 2, Glu-407 to Glu-413, L0754; 2, L0603; 2, SC Tyr-419 to Ser-424, 2, H0170; 1, H0657; 1, H05435 to Gln-444, S0212; 1, H0638; 1, SC 1, H06431; 1, H0533; 1, T H0431; 1, H0575; 1, S0049; 1, H0647; 1, SC 1, H0640; 1, H0551; 1, T 1, H0640; 1, H0551; 1, T 1, H069; 1, T0042; 1, SC 1, H0652; 1, H0652; 1, H0660; 1, H0672; 1, S0369; 1, H0660; 1, H0672; 1, S0350; 1, H0672; 1, S0350; 1, H0672; 1, S0350; 1, H0672; 1, S0031; 1, L0759; 1, L0759; 1, L0757; 1, L0759; 1, S0026; 1, S0031; 1, L0759; 1, S0036; 1 and S00424; 1.	Met-1 to Thr-7, Glu-13 to Val-18, Val-25 to Asn-34, Gly-56 to Val-63, Gln-80 to Glu-89,
	288 129 - 1693 551
·	HWEAC64 784039 2
	278 HW

	79-99,
H0694: 29, H0703: 13, H0683: 10, H0717: 7, H0713: 6, H0542: 6, H0687: 4, H0656: 3, H0685: 2, H0716: 2, H0688: 2, H0695: 2, S0428: 2, H0689: 2, H0684: 2, H0521: 2, H0580: 1, H0601: 1, H0592: 1, H0708: 1, S0150: 1, H0699: 1, H0519: 1, H0709: 1, H0522: 1, H0555: 1, S0028: 1, H0707: 1 and H0543: 1.	AR104: 33, AR033: 30, AR066: 17, AR039: 15, AR096: 14, AR089: 14, AR053: 12, AR052: 10, AR055: 9, AR061: 5 S0422: 20, S0408: 10, L0776: 8, S0444: 7, H0038: 7, S0358: 6, L0740: 6, L0754: 6, L0758: 6, S0440: 5, L0771: 5, S0374: 5, L0756: 5, L0757: 5, L0774: 4, L0519: 4, H0547: 4, H0660: 4, L0748: 4, L0750: 4, L0752: 4, S0436: 4, S6024: 3, S0312: 3, S0442: 3, S0354: 3, T0115: 3, H0327: 3, S0003: 3, T0042: 3,
Lys-102 to Leu-111, Gln-114 to Gln-119.	Met-1 to Arg-15.
	1694
	14 - 433
	588
·	784159
	HSDFQ43
	279

WO 01/90304 PCT/US01/16450 H0264: 1, H0413: 1, H0056: H0051: 1, H0375: 1, S6028: 10428: 1, H0039: 1, H0119: H0032: 1, H0383: 1, H0316: .0665: 1, H0724: 1, H0520: H0689: 1, H0711: 1, H0683: 10445: 1, H0343: 1, H0595: 30049: 1, T0110: 1, H0050: H0036: 1, S0010: 1, S0346: .0389: 1, L0803: 1, L0805: 0636: 1, L0517: 1, L0518: S0152: 1, H0696: 1, S0044: H0627: 1, S0390: 1, S0037: .0764: 1, L0773: 1, L0768: S0144: 1, S0210: 1, L0520: , H0031: 1, H0553: 1, , H0040: 1, T0067: 1, , H0478: 1, H0626: 1, ", T0048: 1, H0421: 1, , S0050: 1, H0015: 1, , S0214: 1, H0328: 1, , H0593: 1, S0126: 1, , S0330: 1, H0518: 1, , L0786: 1, S0260: 1, L0387: 1, L0649: 1, L0590: 1, H0667: 1 , H0560: 1, H0359: 1 , L0769: 1, L0638: L0653: 1, L0655: 1 L0809: 1, L0664: 1

	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,																										
	83-104,	106-122,	51-52, 58-	†								•	185-204,	101-117													
-																	 ;-						_				
S0424:	29,	- 52,		ر بر	<u> </u>		S0358:	1,	H0090:	1,	T0666:	98: 1.	49,	34,	29,	20,	15		L0662:	3,	H0591:	2,	L0663:	2,	L0755:	2,	H0423:
H0216: 1, H0422: 1, S0424: 1 and H0506: 1.	AR053: 38, AR096:	AR052: 27, AR039: 25,	89: 12, AKU33: 60: 10 AB104:	00: 10, AK104: 23: 8 A POC1:	33: 8, AKU01:	L0662: 2, L0751: 2,	.0591: 2, H0265: 1, S0358:	1, H0331: 1, H0486: 1,	H0286: 1, H0644: 1, H0090:	1, H0100: 1, S0142: 1,	.0638: 1, L0648: 1, L0666:	, L0748: 1 and S0398: 1	AR104: 52, AR061: 49,	AR060: 41, AR055: 34,	33: 30, AR089:	AR052: 21, AR039: 20,	AR053: 19, AR096: 15	L0731: 9, L0794: 8	L0749: 6, L0439: 5, L0662:	4, L0770: 3, L0803: 3	L0596: 3, L0717: 2, H0591:	2, L0761: 2, L0766: 2	L0659: 2, L0809: 2, L0663:	2, H0436: 2, L0748: 2	.0747: 2, L0779: 2, L0755:	2, L0758: 2, L0759: 2,	L0591: 2, L0581: 2, H0423:
H02]		AKO	ARU	ARO	AKO	<u> </u>	L059	1, H(H028	1, H(F007	1, L0					•		L074	4, TO	1059	2, L0	<u>1065</u>	2, HC	L074	2, I.0	L059
	Ser-16 to Asp-23.												Asp-25 to Glu-47,	Thr-88 to Gln-99,	Tyr-129 to Ser-135,	Glu-143 to Ile-150,	Pro-216 to Asp-221,	Lys-287 to Ser-293.									
	1695												1696											,			
	45 - 464												123 -	1055													
	290												291														
	784650												784764														
	HMHBN86				_								HLTAZ78														
	280												281		-												

	10-37, 185-214, 39-63, 117-134
2, H0170: 1, S0282: 1, H0661: 1, H0662: 1, H0638: 1, S0418: 1, S0356: 1, S0360: 1, S0046: 1, H0393: 1, H0486: 1, H0147: 1, H0318: 1, L0041: 1, H0562: 1, H0049: 1, H0266: 1, H0124: 1, H0598: 1, H0900: 1, L0475: 1, H0561: 1, S0382: 1, S0440: 1, H0509: 1, H0641: 1, S0002: 1, S0426: 1, L0769: 1, L0764: 1, L0804: 1, L0650: 1, L0805: 1, L0776: 1, L0789: 1, L0665: 1, H0520: 1, H0519: 1, H0666: 1, S0146: 1, S3014: 1, L0754: 1, L0757: 1, L0608: 1, S0026: 1, S0192: 1 and H0542: 1.	AR061: 134, AR039: 81, AR096: 49, AR053: 35, AR104: 34, AR033: 32, AR060: 31, AR089: 30, AR052: 28, AR055: 18 L0766: 5, L0637: 2, L0748: 2, L0777: 2, H0170: 1, S0346: 1, H0560: 1, H0509: 1, S0002: 1, L0764: 1, L0804: 1, L0775: 1, L0789: 1, L0666: 1, S0380:
	2 1326 - 1697 655
	282 HLDBM50 784930 292

WO 0	1/9030																						_	1/(30	1/16	943
·	77-94																										
	303100,	309605,	314580					,																			
	Xq13.3- Xq21.2	7:17hx7																							,		
1, H0521: 1, L0779: 1 and L0755: 1.	9, AR033: 8, 8, AR053: 6			AR060: 4, AR061: 2	L0521: 26, S0422: 22,	H0170: 16, H0144: 16,	L0748: 12, H0083: 11,	H0624: 8, L0747: 7, H0171:	6, L0750: 6, T0042: 5,	L0803: 5, L0749: 5, H0543:	5, H0581: 4, L0794: 4,	L0529: 4, S0134: 3, H0486:	3, L0586: 3, H0013: 3,	T0041: 3, L0517: 3, H0659:	3, L0777: 3, L0755: 3,	L0589: 3, L0599: 3, H0542:	3, H0329: 2, H0645: 2,	H0393: 2, H0427: 2, H0052:	2, H0530: 2, S0036: 2,	H0591: 2, H0063: 2, L0598:	2, L0637: 2, L0662: 2,	L0804: 2, L0655: 2, H0519:	2, L0740: 2, L0752: 2,	L0759: 2, H0583: 1, S0282:	1, H0306: 1, H0402: 1,	H0489; 1, H0580: 1, H0151:	1, H0370: 1, H0392: 1,
	Thr-10 to Asp-20,	Ala-71 to Asp-77.														٠											
	1698																			-							
	104 -	717																									-
	293																										
	785013																										
	ннернзз	-																									
	283																										

	1-26, 53- 75, 83-99	142-160
·		
H0497: 1, S0280: 1, S0010: 1, S0346: 1, L0105: 1, H0421: 1, H0009: 1, H0569: 1, H0050: 1, H0050: 1, H0050: 1, H0050: 1, H0052: 1, H0052: 1, H0052: 1, H0050: 1, H0050: 1, H0050: 1, L0550: 1, L0550: 1, L0555: 1, L0659: 1, L0541: 1, L0542: 1, L0542: 1, L0542: 1, L0542: 1, L0543: 1, L0743:	AR053: 28, AR033: 20, AR052: 17, AR089: 12, AR096: 10, AR104: 10, AR060: 7, AR039: 5, AR055: 4, AR061: 4 H0171: 1, S0132: 1, H0528: 1 and L0592: 1.	AR055: 8, AR060: 5, AR052: 4, AR033: 4, AR061: 4, AR053: 4, AR096: 3, AR089: 3,
	lle-42 to Gln-52.	Ser-12 to Gln-19.
	1699	1700
	139 - 462	61 - 588
	294	295
	785497	785958
	HAIDL86	HTEPF14
	284	285

	85-104	47-73
AR104: 3, AR039: 2 L0758: 2, S0134: 1, H0618: 1, H0038: 1 and H0616: 1.	AR052: 14, AR053: 8, AR055: 8, AR089: 8, AR096: 7, AR033: 7, AR060: 7, AR039: 5, AR061: 5, AR104: 4 S0126: 2, S0474: 1 and S0003: 1.	AR052: 41, AR089: 44, AR052: 41, AR053: 38, AR096: 35, AR104: 30, AR060: 27, AR039: 16, AR055: 16, AR061: 8 S0358: 8, L0766: 7, L0777: 7, L0731: 7, L0803: 4, L0659: 4, L0748: 4, L0751: 4, S0250: 3, L0775: 3, L0783: 3, L0809: 3, L0663: 3, H0305: 2, S0418: 2, S0360: 2, S0010: 2, L0763: 2, L0789: 2, H0520: 2, S3012: 2, L0750: 2, L0752: 2, L0755: 2, L0599: 2, L0362: 2, S0242: 2, H0717: 1, H0583: 1, H0656: 1, S0212: 1, S0420: 1,
	Val-78 to Asp-85.	Leu-28 to Arg-38.
	1701	1702
	363 -	150 - 449
	296	297
	786659	786830
	HOEDD04 786659	HODBK89
	286	287

	T
	85-101, 41-57, 66- 82
S6026: 1, 1, 10, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	1, 0, 0, 0, H0581:
S0376: 1, H0208: 1, S6026: 1, H0574: 1, H0532: 1, S0414: 1, H0559: 1, H0486: 1, H0013: 1, H0575: 1, S0474: 1, H0581: 1, H0570: 1, H0024: 1, H0014: 1, H0555: 1, H0029: 1, H0551: 1, H0569: 1, H0551: 1, H0569: 1, L0761: 1, L0372: 1, L0520: 1, L0774: 1, L0659: 1, L0650: 1, L0774: 1, L0653: 1, L0659: 1, L0666: 1, L0665: 1, H0684: 1, L0666: 1, L0665: 1, H0684: 1, L0793: 1, L0745: 1, L0793: 1, L0745: 1, L0749: 1, L0746: 1, H0543:	AR089: 1, AR033: 1, AR061: 0, AR104: 0, AR096: 0, AR055: 0, AR039: 0, AR060: 0, AR052: 0 L0740: 6, S0212: 3, H0265: 2, H0656: 2, H0581:
S03 /6: 1, 803 /6: 1, 1, 10574 S0414: 1, 1, 1, 10013 S0414: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	AR089: AR061: AR096: AR039: AR052: L0740: 6 H0265: 2,
	Met-1 to Ile-11, Asn-16 to Gly-33.
	1703 M. A.
-	182 - 529
·	298
	786878
	HMUAZ89
	288

	282-308	63-89, 48- 64
	,	300047, 300071,
		Xp11.23
2, H0038: 2, H0529: 2, L0649: 2, S0027: 2, L0754: 2, L0777: 2, L0731: 2, L0599: 2, S0192: 2, S0134: 1, H0341: 1, H0663: 1, S0418: 1, S0045: 1, H0619: 1, H0497: 1, H0486: 1, L0471: 1, H0615: 1, H0553: 1, H0040: 1, H0551: 1, L0662: 1, L0766: 1, L0803: 1, L0654: 1, L0658: 1, H0435: 1, H0660: 1, S0390: 1, S3014: 1, S0206: 1, L0750: 1, L0752: 1, S0194: 1 and H0506: 1.	AR104: 32, AR033: 24, AR096: 24, AR052: 23, AR053: 22, AR055: 20, AR039: 17, AR089: 15, AR060: 13, AR061: 9 L0758: 7, L0779: 5, H0038: 4, H0616: 2, L0151: 2, L0766: 2, H0125: 1, T0040: 1, H0050: 1, H0144: 1, H0698: 1, L0438: 1, H0521: 1, L0777: 1, L0752: 1, L0759: 1 and S0260: 1.	AR039: 43, AR053: 31, AR033: 30, AR089: 24,
	Arg-64 to His-70.	1705 Asp-26 to Arg-32.
	1704	1705
	221 - 1144	21 - 416
		300
	787263	787450
	HSBBB92	HHBGJ75
	289	290

			304																										
300110,	300600,	301000.	301000,	301830,	309470,	309500,	309610,	309850,	311050,	312060													- · · · ·						
AR052: 23, AR055: 21,	AR096: 20, AR104: 20,	R060: 15, AR061: 12	L0741: 7, H0545: 6,	.0770: 6, L0758: 5, S0045:	3, L0769; 3, L0794; 3,	.0766: 3, L0805: 3, L0809:	3, H0689; 3, L0777; 3,	.0592: 3, S0360: 2, H0156:	2, S0010: 2, H0009: 2,	S0022: 2, H0135: 2, H0100:	2, H0538: 2, S0126: 2,	0759; 2, L0596; 2, L0588;	2, L0589: 2, S0040: 1,	S0212: 1, H0484: 1, H0483:	l, H0255: 1, H0662: 1,	S0442: 1, S0046: 1, H0351:	l, H0441: 1, H0431: 1,	H0486: 1, H0052: 1, H0309:	, H0546: 1, H0566: 1,	.0471: 1, H0373: 1, S0388:	,, S0051: 1, H0083: 1,	H0354: 1, H0594: 1, H0266:	l, H0288: 1, H0328: 1,	H0615: 1, H0428: 1, H0030:	l, H0031: 1, H0628: 1,	H0124: 1, S0036: 1, H0551:	1, T0004: 1, S0210: 1,	.0369: 1, L0768: 1, L0803:	, L0650: 1, L0776: 1,
A	A		I	27	3	27	3,	<u> </u>	,	08	- 2	071		08	•	08)H	1,		1,)H)H	1	HC HC		<u></u>	

	91-121, 77-93	80-97, 132-148, 111-127	248-264, 114-130
L0518: 1, L0791: 1, H0682: 1, H0539: 1, S0044: 1, H0436: 1, S3012: 1, S0027: 1, L0740: 1, L0754: 1, L0747: 1, L0756: 1, L0780: 1, S0031: 1, L0599: 1, H0665: 1, S0192: 1, H0543: 1 and H0423: 1.	AR053: 1, AR055: 1, AR089: 1, AR033: 1, AR061: 0, AR096: 0, AR039: 0, AR104: 0, AR052: 0, AR060: 0 H0543: 2, H0656: 1, H0341: 1, S0045: 1, H0039: 1, S0210: 1 and H0521: 1.	AR096: 8, AR033: 7, AR053: 6, AR060: 5, AR089: 5, AR052: 5, AR039: 3, AR055: 2, AR061: 2, AR104: 1 S0007: 2, T0040: 1, S0010: 1, H0374: 1, L0157: 1, H0488: 1, H0519: 1 and H0539: 1.	AR055: 10, AR096: 6, AR060: 6, AR033: 6, AR052: 5, AR089: 5, AR061: 4, AR053: 4,
	Lys-26 to Glu-32, Leu-36 to Thr-43, Ala-64 to Trp-70.		Tyr-21 to Lys-28, Asp-51 to Asn-61, Asp-83 to Val-98, Phe-157 to Gln-165,
	1706	1707	1708
	78 - 608	570 - 1073	105 - 1220
	301	302	303
	787466	787587	788955
	HDPRY 22	HBBBC20	HMELW08
	291	292	293

	190-207, 14-30, 288-304, 144-160	161-177, 276-292
Arn-198 to Asn-205, AR104: 3, AR039: 3 Arg-241 to Gly-247, L0439: 4, H0553: 3, Thr-266 to Leu-272, S0414: 2, H0031: 2, H0625: Gln-288 to Lys-299, 2, H0529: 2, H0144: 2, Pro-348 to Gly-354. S0126: 2, L0742: 2, L0744: 2, L0779: 2, H0717: 1, H0656: 1, S0222: 1, H0333: 1, H0013: 1, S0010: 1, T0110: 1, H0050: 1, T0010: 1, S6028: 1, H0551: 1, H0100: 1, T0042: 1, S0344: 1, H0538: 1, L0766: 1, L0805: 1, L0665: 1, H0519: 1, H0690: 1, H0670: 1, S0380: 1, L0743: 1, L0756: 1, L0731: 1, S0026: 1, L0731: 1, S0276: 1, H0423: Land L0698: 1.	AR039: 69, AR096: 52, AR089: 45, AR052: 34, AR053: 32, AR060: 21, AR055: 15, AR104: 13, AR033: 12, AR061: 8	Pro-15 to Gly-23, AR055: 11, AR061: 6, Glu-59 to Ser-64, AR060: 6, AR033: 5, Leu-100 to Gln-106, AR089: 4, AR052: 4,
Asn-198 Arg-241 Thr-266 Gln-288 Pro-348	1709	1710 Pro-15 t Glu-59 t Leu-100
	150 -	1095 - 82
	304	305
	789115	789276
	HTPDL90	HTACZ08
	294	295

	52-72, 31- 50, 75-95, 9-28
AR096: 3, AR104: 3, AR053: 3, AR104: 3, L0766: 4, L0749: 4, L0804: 3, L0751: 3, H0486: 2, H0069: 2, H0012: 2, H0620: 2, H0634: 2, H0616: 2, L0771: 2, H0534: 2, H0616: 1, H0255: 1, S0356: 1, H0618: 1, H0619: 1, H0609: 1, H0618: 1, H0638: 1, H0618: 1, H0638: 1, L0761: 1, L0769: 1, L0774: 1, L0775: 1, L066: 1, L0665: 1, S0126: 1, L0526: 1, L0790: 1, L0779: 1, L0756: 1, S0126: 1, L0756: 1, L0779: 1, L0757: 1, L0758: 1, L0779: 1, L0757: 1, L0779: 1, L0757: 1, L0758:	1 and S0194: 1. AR096: 18, AR039: 18, AR089: 16, AR060: 12, AR104: 11, AR053: 10, AR052: 10, AR033: 9, AR055: 9, AR061: 5 S0114: 2, S0360: 1,
Arg-134 to Giu-139, ARU96: 3, AR104: Met-219 to Trp-225, AR053: 3, AR039: Ile-255 to Asp-260. L0766: 4, L0749: 4 L0804: 3, L0751: 3, 2, H0069: 2, H0012: H0620: 2, H0634: 2, 2, L0771: 2, H053: 1, 1, H0255: 1, S0356: S0376: 1, H0619: 1, 1, H0613: 1, H0586: H0618: 1, H0733: 1, 1, L076: 1, L0769: 1, 1, L076: 1, L0769: 1, 1, L0774: 1, L0775: L0651: 1, L0665: S0126: 1, L0656: 1, 1, L0779: 1, L0757: 1, 1, L0750: 1, L0757: 1, 1, L0779: 1, L0757: 1,	
	1711
·	48 - 377
	306
	789377
	HAGEC91
	296

	451-468, 2-18, 474- 490, 306- 322
1, S0010: 1, H0538: 1, L0527: 1, L0657: 1, L0659: 1, H0435: 1, H0658: 1, H0543: 1 and L0600: 1.	AR039: 45, AR096: 22, AR104: 20, AR033: 19, AR053: 18, AR089: 16, AR055: 15, AR060: 14, AR055: 15, AR060: 14, AR052: 13, AR061: 8 L0666: 5, L0748: 5, L0747: 4, L0768: 3, H0521: 3, L0750: 3, L0755: 3, L0608: 3, H0486: 2, H0024: 2, H0052: 2, H0487: 2, L0665: 2, L0766: 2, L0665: 2, H0638: 2, H0647: 1, H0658: 1, H0648: 1, H0656: 1, H0646: 1, S0250: 1, S0003: 1, H0648: 1, H0059: 1, H0649: 1, H0591: 1, H0649: 1, H0591: 1, H0649: 1, H0569: 1, L0763: 1, L0662: 1, L0662: 1, L0662: 1, L0662: 1, L0669: 1, L0775: 1, L0669: 1, L0783: 1, L0869: 1, L0775: 1, L0869: 1, L0783: 1, L0889: 1, L0783: 1, L0889: 1, L0783: 1, L0889: 1, L0783: 1, L0889: 1, L0783: 1, L0783: 1, L0889: 1, L0783:
	Trp-105 to Thr-116, Trp-155 to Gln-162, Gln-177, Gln-226 to Glu-232, Gln-254 to Glu-260, Glu-296 to Tyr-308, Thr-338 to Val-344, Leu-377 to Ile-384, Asp-413 to Lys-419, Cys-436 to Ile-443, Thr-490 to Gln-496, Glu-508 to Ser-514, Lys-525 to Glu-537.
	1712
	1698 - 10
	307
	789555
	HTTCB23

	82-98	116-134	84-100
L0789: 1, L0664: 1, H0519: 1, H0648: 1, S0378: 1, S0380: 1, H0522: 1, L0779: 1, L0759: 1, H0543: 1 and H0423: 1.	AR039: 33, AR089: 18, AR053: 17, AR096: 17, AR033: 14, AR052: 14, AR104: 13, AR060: 11, AR055: 7, AR061: 5 H0583: 1 and S0216: 1.	AR055: 3, AR061: 3, AR033: 3, AR096: 3, AR060: 2, AR089: 2, AR052: 1, AR053: 1, AR039: 1, AR104: 0 H0618: 3, H0253: 3, L0803: 2, L0748: 2, L0779: 2, L0758: 2, H0550: 1, T0060: 1, H0544: 1, H0041: 1, S0368: 1, H0038: 1, H0509: 1, L0363: 1, L0768: 1, L0657: 1, L0809: 1, L0663: 1, H0684: 1 and S0152: 1.	AR055: 20, AR052: 18, AR033: 17, AR104: 16, AR039: 15, AR053: 14, AR060: 13, AR096: 9,
,			Gly-42 to Gly-47, Asn-64 to Asn-74, Ser-102 to Val-108, Pro-114 to Leu-121.
	1713	1714	1715
	99 -	121 - 576	4 - 513
	308	309	310
	789607	099682	789688
	HYAAL21	нт.г.н.ү 91	HUTAD91
	298		300

i

	114-130	235-252, 133-149
AR089: 8, AR061: 3 L0731: 6, L0770: 3, H0295: 2, L0375: 2, L0756: 2, H0706: 1, H0212: 1, S0440: 1, L0369: 1, L0763: 1, L0769: 1, L064: 1, L0646: 1, L0764: 1, L0774: 1, L0805: 1, L0542: 1, L0783: 1, L0666: 1, L0664: 1, L0565: 1, H0648: 1, S0027: 1, L0740: 1, L0745: 1, L0749: 1, L0750: 1, L0752: 1, L0599: 1 and H0423: 1.	AR096: 3, AR089: 2, AR060: 2, AR104: 2, AR053: 2, AR055: 2, AR033: 1, AR052: 1, AR061: 1, AR039: 0 H0538: 1, L0803: 1 and L0731: 1.	AR033: 7, AR096: 5, AR052: 4, AR060: 4, AR061: 3, AR089: 3, AR055: 3, AR053: 2, AR104: 2, AR039: 1 H0521: 4, H0656: 3, H0542: 2, L0615: 1, S0045: 1, H0643: 1, H0013: 1,
	Pro-5 to Lys-16, Ser-21 to Leu-26, Trp-43 to Cys-53, Glu-74 to Pro-81, Met-86 to Val-91.	Asp-41 to Asn-47, Ser-57 to Lys-63, Glu-91 to Gly-98, Asp-108 to Cys-117, Lys-177 to Glu-187, Phe-204 to Asp-221.
	1716	1717
	28 - 531	50 - 1051
_	311	312
	790091	790219
,	HKGDE58	HBIAW78
	301	302

50-73,	74-90, 12-
	180069, 180069, 180069, 201450, 248610,
	1p31
H0575: 1, H0581: 1, H0421: 1, S0049: 1, H0052: 1, T0103: 1, H0050: 1, H0373: 1, H0051: 1, H0050: 1, H0039: 1, H00375: 1, H0056: 1, H0039: 1, H0030: 1, H0042: 1, H0042: 1, H0042: 1, H00494: 1, S0150: 1, S0344: 1, S0210: 1, S0422: 1, H0519: 1, H0522: 1, S3012: 1, L0588: 1 and L0591: 1. AR051: 2, AR052: 2, AR053: 1, H0054: 4, L0766: 2, L0777: 2, H0549: 1, H0093: 1, H0135: 1, H0087: 1, H0264: 1, L0769: 1, L0804: 1, L0774: 1, L0789: 1, L0778: 1, L0778: 1, L0778: 1, L0789: 1, L0778: 1, L0789: 1, L0787: 1, L0789: 1, L0789: 1, L0787: 1, L0789: 1, L0789: 1, L0787: 1, L0789: 1, L0787: 1, L0789: 1, L0789: 1, L0787: 1, L0789: 1, L0787: 1, L0789: 1, L0787: 1, L0789: 1, L	1 and L0666: 1. AR039: 4, AR096: 3, AR089: 3, AR104: 3, AR033: 2, AR060: 2, AR055: 2, AR052: 2, AR061: 2, AR053: 2
	Phe-6 to Leu-14, Lys-30 to Asp-37.
1718	1719
89 - 853	141 - 446
313	314
790634	790790
HTOIC11	304 HNTRM40 790790
303	304

	160-188, 20-47, 200-223, 57-84, 132-150, 2-18	95-113, 38-54
600309, 601 <i>6</i> 76, 602522		
58: 251: 44:	22: 21: 1.	57:
L0770: 4, H0551: 2, L0805: 2, H0593: 2, H0658: 2, L0439: 2, L0747: 2, H0431: 1, H0156: 1, H0251: 1, H0135: 1, L0776: 1, L0537: 1, L0790: 1, H0144: 1, L0352: 1, H0547: 1, S0037: 1, S0206: 1, L0755: 1 and L0758: 1.	AR055: 7, AR096: 5, AR060: 4, AR052: 4, AR089: 3, AR033: 3, AR104: 2, AR039: 1 L0527: 2, H0208: 1, H0635: 1, S0250: 1, H0622: 1, H0644: 1, H0551: 1, L0766: 1, H0519: 1, H0521: 1, S0027: 1 and H0136: 1.	AR055: 14, AR033: 11, AR053: 11, AR089: 10, AR052: 9, AR096: 8, AR039: 8, AR060: 8, AR061: 7, AR104: 7 H0620: 7, L0731: 6, L0751: 4, H0599: 3, L0157: 3, H0135: 3, L0747: 3, L0779: 3, S0222: 2, H0333: 2, H0012: 2, H0188: 2,
	Pro-98 to Phe-110, Al Ser-114 to Asp-123, Al Lys-152 to Arg-157, Al Arg-235 to Gin-250, Al I I I I I I I I I I I I I I I I I I I	1 Gly-33 to Arg-38. Al Al Al Al LC LC LC 2,
· · · · · · · · · · · · · · · · · · ·	1720	1721 0
	1645	149 - 505
	315	316
	790807	791489
	HSKAY30	HSSIN12
	305	306

	53-69	157-173
1		
H0213: 2, H0553: 2, L0142: 2, L0519: 2, L0791: 2, H0690: 2, L0743: 2, L0749: 2, L0752: 2, L0759: 2, L0752: 2, L0759: 2, L0752: 2, L0759: 2, L0752: 2, L0759: 2, L0759: 2, L0752: 1, H0648: 1, L0055: 1, H0549: 1, H0052: 1, H0056: 1, S0388: 1, H0059: 1, S0038: 1, H0059: 1, S0038: 1, H0646: 1, L0769: 1, L0664: 1, L0769: 1, L0664: 1, L0769: 1, L0664: 1, L0769: 1, L0750:	AR033: 19, AR089: 15, AR053: 9, AR039: 9, AR055: 9, AR096: 8, AR060: 8, AR052: 7, AR061: 7, AR104: 6	AR033: 3, AR096: 3, AR053: 3, AR052: 3,
	Ser-16 to Gly-22.	23 Arg-56 to Lys-73, Arg-86 to Asp-92,
	1722	1723
	136 - 483	196 - 921
	317	318
	791501	791776
	HTFBG93	HCH0084
	307	308

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AR055: 2, AR104: 2, AR060: 2, AR089: 1, AR039: 1, AR061: 1	L0438: 6, L0439: 6, L0755: 4, L0776: 3, L0754:	3, H0542: 3, H0556: 2, 1 0157: 2 H0553: 2 1 0770:	L0769: 2, L0805: 2,	L0748: 2, L0747: 2, L0749:	L0750: 2, L0779: 2,	.0731: 2, S0242: 2, H0265:	l, L0426: 1, H0341: 1,	H0484: 1, S0418: 1, S0046:	H0393: 1, S0278: 1,	S0222: 1, H0013: 1, H0635:	1, H0427: 1, H0156: 1,	0575: 1, L2250: 1, H004	l, H0009; 1, H0050: 1,	.0471: 1, H0266: 1, H0328:	l, H0428: 1, H0644: 1,	H0212: 1, H0591: 1, H0616:	1, H0412: 1, T0041: 1,	S0438: 1, H0647: 1, S0426:	L0771: 1, L0636: 1,	L0789: 1, L4501: 1, L0666:	1, L0665: 1, H0520: 1,	H0519: 1, H0593: 1, H0435:	H0658: 1, S0152: 1,	H0214: 1, H0478: 1, S0027:	1, S0028: 1, L0756: 1,
Glu-103 to Arg-109, A Ser-146 to His-154, A Pro-190 to Ile-195, A	— <u>−</u> =	3,	, S	<u> </u>	2,	<u> </u>		茁	1,	SC	1,	H	1,	Ä	1,	H	1,	SC	1,	ĭ	Ţ,	Ħ	1,	<u>出</u>	1,
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MO 01	7903																							_		501	
,	137-154							308-325,	64-80,	211-227,	158-174	 ,											·				
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L0752: 1, H0343: 1 and S0436: 1.	1	AR060: 10, AR039: 9,		AR089: 6, AR033: 6,	5, AR053:	H0624: 1, H0171: 1 and	H0013: 1.	AR096: 3, AR052: 3,	AR053: 3, AR033: 3,	AR039: 2, AR089: 2,	AR104: 2, AR060: 1,	AR061: 1, AR055: 1	L0439: 11, L0666: 5,	L0740: 5, H0580: 4, H0591:	4, H0519: 4, S0476: 3,	L0471: 3, H0553: 3, L0770:	3, L0803: 3, L0752: 3,	L0592: 3, S0418: 2, H0013:	2, H0046: 2, H0373: 2,	S0003: 2, H0090: 2, H0551:	2, H0412: 2, S0386: 2,	.0775: 2, L0655: 2, L0663:	2, L0665: 2, H0547: 2,	H0660: 2, H0521: 2, L0748:	2, L0751: 2, L0754: 2,	L0747: 2, L0731: 2, L0757:	2, L0759: 2, L0608: 2,
		Arg-55 to Gln-71, \not		۰î	~ <u>.</u>			Asp-3 to Ile-14, △	∞ <u>`</u>			Arg-116 to Gly-121, A			Asp-271 to Glu-276, 4			Leu-370 to Gln-375, L	Glu-407 to Thr-412, 2	Ile-421 to Leu-429. S	2	<u> </u>	2		2		2
	1724							1725		•						, '											
	171 -	<i>LL</i> 9						24 -	1412				····							-							
	319						_	320																			
	791839							792393						•													
	HE8OX93							HOFMV90									·					-				,	•
	309						į	310																			

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											-								-										
71:		13:		26:		22:		.98	_	03:		71:		52:		(00:		92:		<u> </u>		72:		35:		. <u>;</u>		28:	
H0543: 2, H0422: 2, H0171:	1, H0556: 1, H0686: 1,	S0040: 1, S0342: 1, H0713:	1, H0717: 1, H0657: 1,	H0125: 1, S03:	1, S0046: 1,	H0619: 1, H0411: 1, S0222:	1, H0497: 1,	T0040: 1, L05	1, S0474: 1,	H0581: 1, H0052: 1, T0103:	l, H0597: 1, H0545: 1,	L0157: 1, H05	1, H0083: 1,	H0266: 1, S0214: 1, H0252:	1, H0379: 1,	T0042: 1, H05	1, H0625: 1, S0440: 1,	H0641: 1, S0422: 1, S0426:	1, L0800: 1,	L5564: 1, L08	1, L0606: 1, L0657: 1,	L0809: 1, L07	1, L0664: 1,	H0693: 1, L0352: 1, H0435:	1, H0658: 1, H0672: 1,	S0380: 1, S015	1, S0027: 1, S0028: 1,	20777: 1, L0755: 1, L0758:	1, S0434: 1, S0436: 1,
H0543: 2,	1, H0556:	S0040: 1,	1, H0717:	S0212: 1,	1, S0358:	H0619: 1,	1, H0415:	H0486: 1,	1, H0575:	H0581: 1,	1, H0597:	L0041: 1,	1, H0057:	H0266: 1,	1, H0040:	H0623: 1,	1, H0625:	H0641: 1,	1, L0763:	L0766: 1,	1, L0606:	L0659: 1,	1, L0532:	H0693: 1,	1, H0658:	S0330: 1,	1, S0027:	L0777: 1,	1, S0434:
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			<u>.</u>									-	-	_	_					_								-	
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	107-123						182-198		,											56-82	-			
									-				•											
L0601: 1, L0366: 1, H0542: 1, H0423: 1 and H0293: 1.	AR089: 9, AR053: 8,	AR033: 8, AR060: 7, AR096: 7, AR061: 6,	3, AR039:	H0038: 2, S0010: 1,	H0252: 1, T0023: 1 and	H0616: 1.	AR055: 8, AR052: 6,	AR060: 5, AR096: 5,	AR089: 4, AR061: 4,	AR039: 3, AR104: 2	H0046: 7, S0314: 2,	L0751: 2, L0754: 2, H0171:	1, S0222: 1, H0574: 1,	H0318: 1, H0194: 1, H0477:	1, S0422: 1, L0373: 1,	L0768: 1, L0776: 1, L0655:	1, L0666: 1, L0747: 1,	L0780: 1, L0752: 1, S0026:	1 and S0424: 1.	AR055: 6, AR053: 3,	AR060: 3, AR096: 3,	AR052: 3, AR061: 3,	AR089: 3, AR033: 2,	AR104: 2, AR039: 1
	Glu-94 to Pro-99.			_			Glu-16 to Thr-24,	Ser-32 to Val-42.	 											Val-13 to Asn-21,	His-24 to Leu-29,	Pro-32 to Pro-37,	Arg-43 to Leu-48,	Cys-83 to Met-94.
	1726						1727													1728				
	61 - 573						813 -	148								·				72 - 374				
	321						322													323				
	792575						792627													792628				
	HTEFV95						HETJA44			,										HE2DR93				
	311						312								•					313				

	126-143
	10, 10, 10, 9, 4 4 00775: 0775: 0769: 0769: 0789:
H0620: 1, 3744: 1 and	11, AR039: 1 10, AR055: 1 10, AR089: 3 7, AR060: 5 5, AR061: 4 3, L0803: 3, LC 2, L0771: 2, LC 2, L0771: 2, LC 2, L0771: 2, LC 2, L0771: 2, LC 3: 2, H0624: 1, H 1, S0442: 1, H 1, H0333: 1, L 1, H0333: 1, L 1, H0179: 1, L 1, H0179: 1, L 1, L0770: 1, LC 1, L0809: 1, LC 2: 1, L0800: 1, LC 3: 1, L0800: 1, LC 4: 1, L0800: 1, LC 5: 1, L0800: 1, LC 1, L0800: 1, LC
H0170: 1, H0620: 1, 20774: 1, L0744: 1 and 20748: 1.	
	Glu-7 to Arg-22.
	1729 (
	41 - 610
	324
	792938
	HAJBT15
	314

	78-94, 124-140, 37-53, 97- 113	98-115, 62-78, 40- 56
		300047, 300062, 300600,
		Xp11.4- p11.1
1, L0666: 1, L0663: 1, H0144: 1, L0438: 1, H0547: 1, H0593: 1, S0126: 1, H0670: 1, S0328: 1, S0330: 1, H0539: 1, H0521: 1, H0696: 1, H0627: 1, L0748: 1, L0749: 1, L0756: 1, L0786: 1, L0780: 1, L0752: 1, H0445: 1, L0605: 1 and L0592: 1.	AR096: 21, AR061: 16, AR089: 11, AR052: 7, AR039: 5, AR055: 4, AR104: 4, AR053: 4, AR060: 4, AR033: 4 H0265: 3, H0556: 3, H0657: 3, H0059: 3, H0255: 2, H0661: 2, L0750: 2, H0662: 1, H0638: 1, H0393: 1, H0101: 1, T0082: 1, T0110: 1, H0578: 1, H0144: 1, H0647: 1, H0606: 1, T0042: 1, S0142: 1, H0144: 1, H0547: 1, H0576: 1, S3014: 1, L0747: 1, L0777:	AR089: 20, AR033: 19, AR104: 15, AR060: 15, AR061: 12, AR039: 11,
	Met-1 to Arg-15, Asp-58 to Ala-63, Pro-67 to Arg-73.	Glu-34 to Asp-39.
		1731
	109 - 606	170 - 532
	325	326
	793148	793204
	HDBAD63	нЕ8QH85
	315	316

VO 01/90304		
309470, 309500, 309610, 310500, 310600,	312060	
	·	
AR055: 10, AR096: 8, AR053: 7, AR052: 7 H0547: 25, H0144: 14, H0619: 13, H0135: 13, H0539: 13, L0747: 13, H0013: 12, L0592: 10,	H0024: 9, L0769: 8, L0754: 8, H00100: 7, H0424: 7, H0100: 7, L0731: 7, H0624: 6, H033: 6, L0774: 6, L0765: 6, L0799: 6, S0027: 6, L0759: 6, L0599: 6, S0420: 5, L0471: 5, H0615: 5, H0170: 4, H0393: 4, H0548: 5, L0594: 5, L0595: 5, H0046: 4, H0050: 4, H0545: 4, H0553: 4, R0050: 4, H0553: 4, L076: 4, L0666: 4, L0751: 4, L0750: 4, L0664: 4, S0126: 4, L0748: 4, L0751: 4, L0750: 4, L0605: 4, H0543: 4, S0192: 4, H0543: 4, S0418: 3, S0358: 3, S0046: 3,	H0586: 3, H0486: 3, H0156: 3, H0581: 3, H0251: 3, H0546: 3, H0081: 3, H0015: 3, H0083: 3, H0687: 3,
	•	

			FC1/0301/10430
	.2: 11:	35. 54. 54. 55. 55. 36. 37. 38. 38. 38. 38. 38. 38. 38. 38. 38. 38	.1: 4: 5:
S0022: 3, H0328: 3, H0428: 3, H0551: 3, L0772: 3, L0764: 3, L0521: 3, L0662: 3, L0768: 3, L0809: 3, S0380: 3, L0439: 3, S0212: 2, H0483: 2, S0356: 2, S0007: 2, H0351: 2, H0610:	2, H0587: 2, H0574: 2, H0318: 2, H0544: 2, H0009: 2, H0373: 2, T0010: 2, S6028: 2, H0266: 2, H0252: 2, H0032: 2, H0673: 2, H0087: 2, L0351: 2, H0641: 2, S0210: 2, L0369: 2,	L0762: 2, L0803: 2, L0775: 2, L0651: 2, L0783: 2, H0599: 2, H0593: 2, H0690: 2, S0152: 2, H06478: 2, S0037: 2, S3014: 2, S0028: 2, L0752: 2, L0756: 2, H0171: 1, H0395: 1, S0040: 1, H0295: 1, S0040: 1, H0295	1, H0294: 1, S0114: 1, S0430: 1, H0484: 1, H0661: 1, H0664: 1, H0662: 1, H0176: 1, S0442: 1, S0354: 1, S0376: 1, S0360: 1, H0208: 1, S0045: 1, H0645: 1, S0300: 1, L0717: 1,

50:	.69:	.:-	72:	75:			42:	ţ	.63:	13.	13.	20:		74:		75:		34:		53:	
H0261: 1, H0549: 1, H0550: 1, S0222: 1, S0220: 1, H0441: 1, H0403: 1, H0438:	1, H0632: 1, T0039: 1, H0244: 1, H0250: 1, H0069: 1, H0427: 1, H0575: 1,	H0374: 1, H0196: 1, H0194: 1, H0085: 1, H0597: 1,	H0327: 1, H0150: 1, H0172: 1, H0123: 1, H0023: 1,	Н0200: 1, Н0051: 1, Н0	1, H0356: 1, H0354: 1, H0271: 1. H0286: 1. H0039:	1, T0006: 1, H0033: 1,	H0604: 1, H0644: 1, L01	1, H0628: 1, H0617: 1,	H0383: 1, H0674: 1, H0163:	1, H0634: 1, H0272: 1, H0268: 1, H0412: 1, H0	60266: 1, 60412: 1, 60413. 1 S0038: 1 T0041: 1	F0042: 1, H0561: 1, S0150:	1, S0144: 1, S0142: 1,	L0638: 1, L0637: 1, L0374:	1, L0773: 1, L0794: 1,	L0649: 1, L0650: 1, L03	1, L0378: 1, L0654: 1,	L0661: 1, L0657: 1, L06	1, L0659: 1, L0636: 1,	L0647: 1, L0367: 1, L0663:	1, H0701: 1, L0438: 1,
											<u> </u>		, ,								

																			. —		

	132-148	65-81
H0689: 1, H0683: 1, H0670: 1, H0660: 1, H0672: 1, S0328: 1, S0330: 1, H0521: 1, S0406: 1, H0555: 1, H0436: 1, L0779: 1, L0780: 1, L0777: 1, H0707: 1, L0589: 1, S0011: 1, H0668: 1, H0653: 1, H0667: 1, H0542: 1, H0669: 1, H0422: 1 and H0506: 1.	AR052: 187, AR053: 127, AR096: 125, AR055: 118, AR089: 96, AR104: 82, AR061: 73, AR060: 73, AR039: 71, AR033: 64 S0418: 2, S0007: 2, S0132: 2, H0559: 2, H0520: 2, H0547: 2, H0650: 1, H0483: 1, S0046: 1, S0476: 1, H0012: 1, H0604: 1, S0366: 1, H0551: 1, S0150: 1, S0378: 1, S0152: 1, S3014: 1, L0439: 1 and S0194: 1.	AR039: 70, AR053: 41, AR104: 39, AR052: 38, AR096: 36, AR033: 36, AR055: 34, AR060: 29, AR089: 24, AR061: 16
	Arg-14 to Ser-23, Arg-50 to Trp-60.	Met-1 to Ala-6, Arg-16 to Thr-28, Leu-34 to Thr-49, Ile-97 to Ile-104, Glu-129 to Arg-137.
	1732	1733
	162 - 662	59 - 469
	327	328
	793373	793433
	HAICU52	HE6BJ49
	317	318

	7 - 7 - 7 - 7 - 7 - 7 - 7 - 7 - 7 - 7 -
	65-85, 5-
L0748: 7, H0039: 5, H0619: 4, L0439: 4, S0222: 3, H0494: 3, L0438: 3, H0012: 2, H0032: 2, H0547: 2, L0740: 2, L0759: 2, H0556: 1, S0134: 1, H0580: 1, S0278: 1, H0415: 1, H0586: 1, T0109: 1, H0013: 1, H0575: 1, S0010: 1, H0581: 1, H0646: 1, L2244: 1, L0471: 1, T0010: 1, H0354: 1, H0644: 1, H0400: 1, H0591: 1, H0038: 1, H0553: 1, H0644: 1, H0623: 1, H0100: 1, S0440: 1, S0344: 1, L0387: 1, L0766: 1, L0790: 1, H0520: 1, H0519: 1, H0660: 1, S0152: 1, S0044: 1, H0436: 1, L0751: 1, L0731: 1, S0031: 1, L0592: 1, S0242:	AR033: 5, AR053: 3, AR052: 3, AR096: 3, AR089: 3, AR061: 3, AR060: 2, AR104: 2, AR039: 2, AR055: 1 L0777: 3, H0013: 2 and L0749: 1.
3, H	Arg-86 to Val-91. ARG ARG ARG ARG ARG LO
	1734 Arg-86
	- 259 - 615
	53 329
•	9 793553
	HE8TJ39
	319

96-112	97-117
53: 3, 56: 1, 51: 1, 51: 1, 53: 0 5: 2, 2, L0659: 11: 2, 2, H0295: 46: 1, 1, H0486: 56: 1, 1, H0561: 54: 1, 1, L0768: 57: 1, 1, S0310: 30: 1, 1, S0436: 43: 1 and	52: 3, 53: 2, 50: 2, 51: 1,
AR052: 3, AR053: 3, AR096: 3, AR055: 2, AR033: 1, AR060: 1, AR089: 1, AR061: 1, AR104: 1, AR039: 0 H0556: 5, H0265: 2, S0418: 2, H0259: 2, S0418: 2, H0259: 2, S0328: 2, L0731: 2, L0759: 2, S0192: 2, H0295: 1, T0049: 1, S0278: 1, H0486: 1, H0250: 1, H0261: 1, H0261: 1, H0261: 1, H0261: 1, L0637: 1, L0639: 1, L0637: 1, L0509: 1, L0638: 1, S0310: 1, H0672: 1, S0330: 1, H0521: 1, S037: 1, L0747: 1, S0434: 1, S0436: 1, L0592: 1, H0543: 1 and H0008: 1.	AR055: 3, AR052: AR089: 2, AR033: AR053: 2, AR060: AR096: 1, AR061: AR104: 1, AR039:
6	
Asp-29 to Thr-34, Val-55 to Gly-65, Glu-114 to Ala-119.	1736 Gly-10 to Pro-19, Pro-25 to Arg-33, Ser-43 to Gly-52.
1735	1736
481	39 - 425
330	331
793632	794297
HFIBG92	HDPBJ94
320	321

254-282, 224-246.	119-140,	160-179,	200-217		40-61, 65-	81								75-99									
											•					-		7,1					
 AR055: 11, AR061: 9, AR033: 9, AR089: 8.	AR052: 8, AR104: 7,		AR060: 5, AR039: 3	H0616: 1, S0150: 1 and L0581: 1.	AR053: 1, AR052: 1,	AR055: 1, AR033: 1,	AR089: 1, AR061: 1,	AR104: 1, AR060: 1,	AR096: 0, AR039: 0	H0255: 1, S0045: 1,	S0278: 1, H0181: 1, H0617:	1, S0428: 1, S0053: 1,	S0028: 1 and L0597: 1.	AR039: 18, AR033: 11,	AR053: 10, AR089: 9,		AR055: 7, AR060: 6,	AR104: 5, AR061: 5	L0666: 8, L0766: 4,	H0038: 3, L0664: 3, L0665:	3, H0265: 2, S0360: 2,	H0046: 2, L0663: 2, H0520:	2, L0748: 2, L0751: 2,
					Arg-8 to Gly-17.	•								Phe-2 to Gln-7.									
1737					1738	,								1739									
342 - 1259					1 - 300								i	883 -	578								
332					333									334									
794354					795325								-	796477			- 						
HPIAX11					HBGMW9	5								HUSI183					-				
322					323									324								•	

WO 01/90304	1 C1/0301/10430
	112-128, 72-88
3358: 0427: 0412: 0646: 0611:	3375: 3390:
2, L0749: 2, L0779: 2, L0777: 2, L0778: 2, H0341: 1, H0638: 1, S0356: 1, S0358: 1, S0045: 1, H0261: 1, S0222: 1, H0632: 1, H0427: 1, H0597: 1, T0010: 1, H0561: 1, S0003: 1, H0412: 1, H0561: 1, S0002: 1, L0646: 1, L0678: 1, L0677: 1, L0659: 1, L0638: 1, L0659: 1, L0638: 1, L0659: 1, L0638: 1, L0659: 1, L0438: 1, H0659: 1, L0438: 1, L0659: 1, L0438: 1, L06547: 1, L0439: 1, L0756: 1, L0777: 1, L0759: 1, L0777: 1, L0	2, AR096: 2, 1, AR060: 1, 1, AR061: 0, 0, AR055: 0, 0, AR039: 0 3, S0001: 2, S0356: 2, L0731: 2, L0361: 1, S0045: 1, S0278: 1, H0250: 1, H0231: 1, L0456: 1, L0375: 1, L04663: 1, L0438: 1, S0390:
2, L0749: 2, L0779: 2, L0777: 2, L0758: 2, H0341: 1, H0638: 1, S0356: 1, S0358: 1, S0045: 1, H0261: 1, S0022: 1, H0632: 1, H0427: 1, H0597: 1, T0010: 1, H0561: 1, S0003: 1, H0412: 1, L0640: 1, L0638: 1, L0646: 1, L0671: 1, L0659: 1, L0651: 1, L0658: 1, L06	AR033: 2, AR096: 2, AR104: 1, AR060: 1, AR089: 1, AR061: 0, AR052: 0, AR055: 0, AR053: 0, AR039: 0 S0028: 3, S0001: 2, S0356 2, H0617: 2, L0809: 2, L0439: 2, L0731: 2, L0361: 2, S0040: 1, S0278: 1, H0250: 1, H0156: 1, H0231: 1, H0181: 1, L0456: 1, L0375: 1, L0783: 1, L0663: 1,
	1740
	55 - 495
	335
	796622
	HBGDP38
	325

		46-64,	1111-12/,	101-00																						62-78, 87-	103
	•		-							_				•	-			•						-			
1. L0747: 1. L0759: 1 and	S0031: 1.	AR053: 19, AR096: 16,	AK052: 16, AK055: 9,	AR060: 6, AR033: 6,	AR039: 3, AR104: 2	L0777: 5, H0265: 2,	H0556: 2, S0358: 2, L0351:	2, L0769: 2, L0766: 2,	L0666: 2, L0748: 2, L0439:	2, H0657: 1, H0255: 1,	H0637: 1, H0549: 1, S0222:	1, H0586: 1, H0427: 1,	H0597: 1, H0545: 1, H0012:	1, S0214: 1, H0424: 1,	H0213: 1, H0628: 1, H0090:	1, H0412: 1, L0637: 1,	L0800: 1, L0644: 1, L0662:	1, L0381: 1, L0776: 1,	L0655: 1, L0659: 1, L0809:	1, L0790: 1, L0792: 1,	L0665: 1, H0547: 1, S0126:	1, H0435: 1, H0670: 1,	S0432: 1, L0749: 1, L0758:	1, H0543: 1, H0423: 1 and	H0422: 1.	AR055: 9, AR060: 5,	AR061: 4, AR033: 3,
		Trp-7 to Gly-21,	Arg-24 to Glu-31,	Arg-129 to Pro-135.	Ser-142 to Phe-147,	Phe-151 to Gly-159.																		-			Arg-29 to Ser-35,
		1741								_																1742	
		195 -	(%/																					٠		1879 -	2349
		336																							-	337	
		798103					-																			799513	
		HTXEC55																								HFXGI63	
		326																								327	

	89-105	225-248, 106-122
		·
01: 39:		666: 57: 521:
AR052: 3, AR089: 3, AR096: 2, AR053: 2, AR104: 2, AR039: 1 S0222: 2, H0100: 2, L0438: 2, S0114: 1, S0001: 1, H0208: 1, H0123: 1, H0012: 1, H0620: 1, S6028: 1, H0328: 1, H0413: 1, S0038: 1, T0042: 1, L0439: 1 and L0593: 1.	1, AR055: 1, 1, AR061: 1, 1, AR052: 0, 0, AR060: 0, 0, AR039: 0	AR096: 1, AR052: 1, AR104: 1, AR060: 1, AR089: 1, AR033: 0, AR055: 0, AR061: 0, AR053: 0, AR039: 0 L0777: 11, L0751: 10, L0769: 7, L0758: 6, L0766: 5, H0617: 4, L0771: 4, L0776: 4, L0439: 4, L0757: 4, L0759: 4, H0253: 3, H0494: 3, L0761: 3, H0521: 3, L0754: 3, H0318: 2, H0150: 2, L0794: 2, L0805:
AR052: AR104: S0222: L0438: 2 1, H0208 H0012: 1 1, H0328 S0038: 1 1 and L0	AR096: 1 AR089: 1 AR033: 1 AR053: 0 AR104: 0 H0560: 2	
Gly-43 to Trp-62, AR052: Gln-107 to Gln-114, AR096: Arg-132 to Lys-140. AR104: S0222: L0438: 2 1, H0208 H0012: 1 1, H0328 S0038: 1	Ser-50 to Pro-55, Asn-62 to Gly-67.	1744 Thr-4 to Pro-28, Pro-51 to His-62, Pro-83 to Thr-91, Phe-100 to Trp-105, Ile-167 to Gln-182.
·	1743	1744
	475	173 - 949
	338	339
	799889	800344
	HAMGW1 9	HDPTA89
	328	329

	25-46, 101-122, 46-62, 126-142
	120550, 120570, 120575, 130500, 133200,
-	1p36.3- p36.2
2, L0665: 2, L0743: 2, L0750: 2, L0752: 2, H0265: 1, S0342: 1, H0713: 1, S0218: 1, L0785: 1, H0484: 1, L0481: 1, S0446: 1, H0637: 1, S0045: 1, H06486: 1, H0649: 1, H06486: 1, H06497: 1, H0599: 1, H0622: 1, H0628: 1, H0629: 1, H0623: 1, H0623: 1, H0623: 1, H0623: 1, H0666: 1, H0662: 1, H0663: 1, H0663: 1, L0796: 1, L0769: 1, L0779: 1, L0779: 1, L0779: 1, L0779: 1, L0789: 1, L0779: 1,	3,
	
	1745
	100 -
,	340
	801935
	HSLDO85
	330

W O 01/90304		U1/1045U
4, 0, 0, 0, δ		
153454, 167410, 236250, 256700, 600975		
<u> </u>		
L0755: 6, L0769: 4, H0009: 3, H0012: 3, L0783: 3, L0749: 3, L0750: 3, L0779: 3, L0731: 3, S0376: 2, H0545: 2, S0051: 2, H0606: 2, H0100: 2, L0638: 2, L065: 2, S0028: 2, L0751: 2, L0747: 2, L0756: 2, L0758: 2, L0603: 2, H0265: 1, H0294: 1, H0341: 1, S0212: 1, S0410: 1, S0045: 1, H0393: 1, H0549: 1, S0222: 1, H0586: 1, H0331: 1, L0623: 1, T0060:	H0331: 1, L0623: 1, T0060: 1, H0581: 1, S0049: 1, H0309: 1, L0471: 1, H0620: 1, H0024: 1, H0266: 1, H0028: 1, H0213: 1, L0456: 1, S0366: 1, S0036: 1, H0040: 1, S0142: 1, L0772: 1, L0372: 1, L0772: 1, L0774: 1, L0775: 1, L0776: 1, L0809: 1, L0519: 1, H0520: 1, H0519: 1, S0126: 1, H0660: 1, S0350: 1, H0660:	50406: 1, H0436: 1, 53012: 1, L0752: 1, L0757: 1, S0436: 1, L0592: 1, S0276:
1, S 1, S 1, S 1, S 1, S 1, S 1, S	HOS HOS HOS HOS HOS HOS HOS HOS HOS HOS	504 1, I S04
		· · · · · · · · · · · · · · · · · · ·
		·····

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	311-330	65-84, 20-
1 and H0422: 1.	AR096: 3, AR089: 2, AR052: 1, AR061: 1, AR033: 1, AR053: 1, AR053: 1, AR060: 1, AR055: 0, AR039: 0, AR104: 0 L0766: 7, L0662: 4, L0789: 4, L0748: 4, L0749: 4, L0769: 3, L0776: 3, L0794: 2, L0666: 2, L0663: 2, R0547: 2, S0360: 2, L0666: 2, L0663: 1, H0657: 1, H0411: 1, H0657: 1, H0411: 1, H0657: 1, L0471: 1, L0163: 1, L0455: 1, L0809: 1, L0387: 1, L0803: 1, L0387: 1, L0518: 1, L0809: 1, L0387: 1, L0696: 1, H0655: 1, L0740: 1, L0742: 1, L0740: 1, L0742: 1, L0740: 1, L0747: 1, L0750: 1, L0757: 1, L0775: 1, L0777: 1, L0777: 1, L0775: 1, L0777:	H0423: 1 and L0600: 1. AR033: 14, AR096: 13,
	Pro-3 to Lys-13, Thr-26 to Thr-41.	Phe-44 to Asn-55,
	1746	1747
	791 - 1792	271 -
	341	342
	805499	805628
	HDQDF38	HULAW69
	331	332

8 E
AR104: 11, AR039: 10, AR061: 9, AR052: 9, AR085: 9, AR060: 8, AR089: 8, AR053: 5 S0278: 15, S0126: 14, L0742: 13, L0754: 11, L0742: 10, L0751: 8, L0747: 8, L0748: 7, H0305: 6, S0360: 6, H0530: 6, H0545: 6, L0776: 6, L0744: 6, H0484: 5, H0638: 5, S0007: 5, S0045: 5, L0750: 5, S0144: 5, L0766: 5, L0805: 5, S0027: 5, L0750: 5, L0757: 5, H0445: 5, H0542: 4, H0087: 4, H0551: 4, S0142: 4, S0344: 4, L0763: 4, L0770: 4, L0764: 4, L0662: 4, L0768: 4, L0763: 4, L0775: 4, H0543: 4, S0040: 3, S0442: 3, S0358: 3, S0408: 3, H0549: 3, H0486: 3, H0544: 3, H0150: 3, H0023: 3, H0510: 3, H0646: 3, L0771: 3, L0773: 3, L0794: 3, L0774:
Arg-86 to Gly-92.
8.29

•				**		3:	-	4		3:	-	-		5:						1:		- 		33:		5:
3, H0422: 3, H0556: 2,	86024: 2, H0295: 2, S011 2, H0341: 2, S0282: 2,	30029: 2, H0661: 2, H058	2, H0441: 2, H0069: 2,	,0021: 2, H0599: 2, T004	2, S0049: 2, H0327: 2,	H0050: 2, H0057: 2, H008	2, H0033: 2, H0213: 2,	HO181: 2, H0606: 2, H06;	2, S0426: 2, L0769: 2,	.0639: 2, L0761: 2, L037	2, L0646: 2, L0378: 2,	.0806: 2, L0517: 2, S005	2, H0670: 2, H0710: 2,	H0522: 2, H0696: 2, L074	2, L0756: 2, L0753: 2,	L0755: 2, L0731: 2, S043	2, S0436: 2, L0588: 2,	H0653: 2, H0667: 2, S019	2, S0196: 2, H0423: 2,	H0352: 2, H0170: 1, H017	l, H0265: 1, H0685: 1,	HO713: 1, H0716: 1, H029	l, S0114: 1, L0002: 1,	H0656: 1, H0381: 1, H04	1, H0402: 1, H0589: 1,	H0125: 1, S0356: 1, H0675
2.61	<u> </u>	<u> </u>					C										CS									
								-																		
	3, H0422: 3, H0556: 2,	3, H0422: 3, H0556: 2, S6024: 2, H0295: 2, S0116: 2, H0341: 2, S0282: 2,	3, H0422: 3, H0556: 2, S6024: 2, H0295: 2, S0116: 2, H0341: 2, S0282: 2, S0029: 2, H0661: 2, H0580:	3, H0422: 3, H0556: 2, S6024: 2, H0295: 2, S0116: 2, H0341: 2, S0282: 2, S0029: 2, H0661: 2, H0580: 2, H0441: 2, H0069: 2,	3, H0422: 3, H0556: 2, S6024: 2, H0295: 2, S0116: 2, H0341: 2, S0282: 2, S0029: 2, H0661: 2, H0580: 2, H0441: 2, H069: 2, L0021: 2, H0599: 2, T0048:	3, H0422: 3, H0556: 2, S6024: 2, H0295: 2, S0116: 2, H0341: 2, S0282: 2, S0029: 2, H0661: 2, H0580: 2, H0441: 2, H069: 2, L0021: 2, H0327: 2,	3, H0422: 3, H0556: 2, S6024: 2, H0295: 2, S0116: 2, H0341: 2, S0282: 2, S0029: 2, H0661: 2, H0580: 2, H0441: 2, H069: 2, L0021: 2, H0599: 2, T0048: 2, S0049: 2, H0327: 2, H0050: 2, H0057: 2, H0083:	3, H0422: 3, H0556: 2, S6024: 2, H0295: 2, S0116: 2, H0341: 2, S0282: 2, S0029: 2, H0661: 2, H0580: 2, H0441: 2, H0699: 2, L0021: 2, H0599: 2, H0327: 2, H0050: 2, H0057: 2, H0083: 2, H0057: 2, H0083: 2, H0033: 2, H0013: 2,	3, H0422: 3, H0556: 2, S6024: 2, H0341: 2, S0116: 2, H0341: 2, S0282: 2, S0029: 2, H0661: 2, H0669: 2, L0021: 2, H0699: 2, H0669: 2, L0021: 2, H0599: 2, H0698: 2, S0049: 2, H0050: 2, H0057: 2, H0050: 2, H0057: 2, H0050: 2, H0051: 2, H0051: 2, H0051: 2, H0666: 2, H0634: 2, H0666: 2, H0666: 2, H0634: 2, H0666: 2, H0666: 2, H0634: 3, H0666: 2, H06	3, H0422: 3, H0556: 2, S6024: 2, H0295: 2, S0116: 2, H0341: 2, S0282: 2, S0029: 2, H0661: 2, H0580: 2, H0661: 2, H0599: 2, T0048: 2, S0049: 2, H0599: 2, H0057: 2, H0050: 2, H0057: 2, H0050: 2, H0634: 2, S0426: 2, L0769: 2, L0769: 2,	3, H0422: 3, H0556: 2, S6024: 2, H0556: 2, S6024: 2, H0541: 2, S0282: 2, S0029: 2, H0661: 2, H0580: 2, H0661: 2, H069: 2, L0021: 2, H0599: 2, T0048: 2, S0049: 2, H0050: 2, H0057: 2, H0050: 2, H0057: 2, H0050: 2, H0051: 2, H0053: 2, H0053: 2, H066: 2, H0634: 2, S0426: 2, L0769: 2, L0769: 2, L0639: 2, L0761: 2, L0373:	3, H0422: 3, H0556: 2, S6024: 2, H0395: 2, S0116: 2, H0341: 2, S0282: 2, S0029: 2, H0661: 2, H069: 2, L0021: 2, H069: 2, L0021: 2, H069: 2, H0050: 2, H0057: 2, H0050: 2, H0057: 2, H0050: 2, H0057: 2, H0050: 2, H0057: 2, H0050: 2, H0050: 2, H0050: 2, H0050: 2, H0050: 2, H0050: 2, L0569: 2, L0566: 2, L0578: 2, L0566:	3, H0422: 3, H0556: 2, S6024: 2, H0341: 2, S0282: 2, H0341: 2, S0282: 2, H0661: 2, H0580: 2, H0661: 2, H0669: 2, L0021: 2, H0699: 2, L0699: 2, L0761: 2, L0769: 2, L07	3, H0422; 3, H0556; 2, S016; 2, H0241; 2, H0292; 2, S0116; 2, H0241; 2, S0282; 2, S0029; 2, H0661; 2, H0580; 2, H0241; 2, H0699; 2, H0641; 2, H0089; 2, H0049; 2, H0049; 2, H0049; 2, H0083; 2, H0033; 2, H0033; 2, H0033; 2, H0634; 2, S0426; 2, L0769; 2, L0769; 2, L0769; 2, L0769; 2, L0646; 2, L0761; 2, L0373; 2, L0646; 2, L0378; 2, L0646; 2, L0378; 2, L0806; 2, L0570; 2, H0670; 2, H0710; 2, H071	3, H0422: 3, H0556: 2, S0024: 2, H0295: 2, S0116: 2, H0295: 2, S0116: 2, H0295: 2, S0116: 2, H0295: 2, H0661: 2, H0580: 2, H0441: 2, H0699: 2, L0761: 2, L0761: 2, L0761: 2, L0373: 2, L0646: 2, L0373: 2, L0806: 2, L0377: 2, S0052: 2, H0670: 2, H0696: 2, L0776: 2, H0696: 2, L0776: 2, H0696: 2, L0776: 2, H0696: 2, L0776: 2, H0670: 2, H0670: 2, H0696: 2, L0775: 2, H06	3, 1402-5; 3, 3012-5; 5, 3016; 5, 4024; 2, 14024; 2, 14025; 2, 30116; 2, 14034; 2, 14024; 2, 14066; 2, 14044; 2, 14069; 2, 14044; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 3, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14069; 2, 14079; 2, 140	3, H0422; 3, H0556; 2, S0116; 2, H0341; 2, S0282; 2, S6024; 2, H0295; 2, S0116; 2, H0341; 2, H0561; 2, H0580; 2, H0661; 2, H0699; 2, L0021; 2, H0699; 3, H0699; 2, L0769; 2, L0769; 2, L0769; 2, L0769; 2, L0769; 2, L0769; 2, L0779; 2, L0806; 2, L0779; 2, H0690; 2, H0690; 2, H0690; 2, H0690; 2, H0690; 2, H0690; 2, L0779; 2, L07796; 2, L0779;	3, H0425; 3, H0556; 2, S0116; 2, H0341; 2, S0282; 2, H0341; 2, S0282; 2, H0641; 2, H0580; 2, H0641; 2, H0692; 3, S00492; 2, H0692; 2, H0692; 2, H0692; 3, H0692; 3, H0692; 3, H0692; 3, H0692; 3, H0692; 3, L0769; 2, H0670; 2, H0710; 2, H0670; 2, H0710; 2, H0670; 2, H0710; 2, H0670; 2, H0710; 2, H0672; 2, H0710; 2, H0672; 2, L0775; 2, L0	3, H042. 3, 1047. 5, 2022. 3, H042. 3, H0556. 2, S0116. 2, H0341. 2, S0282. 2, S0029. 2, H0691. 2, H0691. 2, H0691. 2, H0691. 2, H0691. 2, H0692. 2, L0738. 2, H0662. 2, L0738. 2, H0667. 2, S0194.	3. H0422: 3, H0556: 2, S0024: 2, H0341: 2, S0028: 2, S0029: 2, H0341: 2, S0028: 2, S0029: 2, H0661: 2, H0580: 2, H0441: 2, H0699: 2, H0069: 2, L0699: 2, L06999: 2, L0699: 2, L06999: 2, L069999: 2, L069999: 2, L069999: 2, L06999999999999999999999999999999999999	3. HO422: 3, HO556: 2, S6024: 2, H0556: 2, S6024: 2, H0295: 2, S0116: 2, H0341: 2, S0282: 2, S0029: 2, H0641: 2, H0580: 2, H0441: 2, H0069: 2, H0641: 2, H0689: 2, H0699: 2, H06	3. HQ42: 3, 1002: 3, 1002: 3, 1002: 3, 1002: 3, 1002: 2,	3. 1042; 3. 10556; 2. 86024; 2, 10556; 2. 86024; 2, 10656; 2. 80029; 2, 10656; 2. 80029; 2, 10661; 2, 10580; 2. 10021; 2, 10639; 2, 10048; 2, 10021; 2, 10639; 2, 10048; 2, 10033; 2, 10021; 2, 10033; 2, 10021; 2, 10033; 2, 10021; 2, 10039; 2, 10769; 2, 10639; 2, 10769; 2, 10639; 2, 10769; 2, 10639; 2, 10769; 2, 10639; 2, 10769; 2, 10639; 2, 10769; 2, 10639; 2, 10769; 2, 10769; 2, 10639; 2, 10771; 2, 10670; 2, 10771; 2, 10670; 2, 10771; 2, 10670; 2, 10771; 2, 10670; 2, 10771; 1, 1077	3. H0423: 3, H0556: 2, S6024: 2, H0595: 2, S0116: 2, H0341: 2, S0282: 2, S0029: 2, H0661: 2, H0580: 2, H0661: 2, H0580: 2, H0661: 2, H0689: 2, L0021: 2, H0641: 2, H0689: 2, L0021: 2, H0689: 2, L0021: 2, H0689: 2, L0038: 2, L0038: 2, L0038: 2, L0068: 2, L0078: 2, L0068: 2, L0078: 2, H0678: 2, S0196: 2, H0678: 2, S0196: 2, H0678: 2, S0196: 2, H0678: 1, H0717: H0718: 1, H0718:	3, H9422; 3, H0556; 2, S6024; 2, H0595; 2, S0116; 2, H0341; 2, H0595; 2, S0116; 3, H0441; 2, H0595; 2, S0116; 2, H0441; 2, H069; 2, H0441; 2, H069; 2, H079; 2, H069; 2, H079; 2, H069; 2, H079; 2, H069; 2, H079; 2, H069; 2, H069; 2, H069; 3, H069; 3, H069; 3, H069; 3, H069; 1, H069; 1, H069; 1, H0698; 1	3, 140422, 3, 14056; 2, 2, 86024; 2, 140245; 3, 80029; 2, 140245; 2, 80116; 2, 140341; 2, 18028; 2, 80029; 2, 140641; 2, 14069; 3, 14069

110708: 1 00123: 1	1, n0/28: 1, 30132: 1, S6022: 1, S0222: 1, H0392:	1, H0607: 1, H0592: 1,	H0586: 1, H0333: 1, H0492:	l, T0114: 1, S0280: 1,	T0082: 1, H0618: 1, H0253:	S0010: 1, H0581: 1,	(0251: 1, H0309: 1, H0234:	1, H0546: 1, H0178: 1,	0567: 1, H0081: 1, H0012:	H0024: 1, H0594: 1,	H0266: 1, H0179: 1, H0416:	H0188: 1, H0290: 1,	0292: 1, S0003: 1, H0252:	1, H0328: 1, S0368: 1,	H0604: 1, H0553: 1, H0673:	l, H0708: 1, H0316: 1,	H0598: 1, H0040: 1, H0063:	, H0264: 1, H0413: 1,	S0038: 1, T0041: 1, H0560:	1, H0625: 1, S0464: 1,	0438: 1, S0440: 1, H0130:	, H0641: 1, H0529: 1,	L0369: 1, L0371: 1, L0772:	, L0800: 1, L0642: 1,	0644: 1, L0645: 1, L0521:	1, L0364: 1, L5564: 1,	.5568: 1, L0523: 1, L0653:	1, L0807: 1, L0527: 1,	0636: 1, L0782: 1, L0809:
	 Χ. τ.	1,	<u> </u>	1,	<u>J</u>	1,	<u> </u>	11		1,	<u>H</u>	1	· E	1,	· 田	<u> </u>		1,	S	Ţ	<u> </u>	1,	<u> </u>	<u> </u>		<u></u>			
			_																					_					
																												_	

	72-96	48-65
1, L0529: 1, L0647: 1, L0664: 1, S0428: 1, S0216: 1, H0144: 1, H0520: 1, H0547: 1, H0689: 1, S0378: 1, S0152: 1, S0406: 1, H0187: 1, H0576: 1, S3012: 1, S0037: 1, S0206: 1, L0740: 1, L0749: 1, L0779: 1, L0759: 1, L0605: 1, L0608: 1, S0106: 1, H0216: 1, S0192: 1 and S0276: 1.	AR055: 8, AR061: 7, AR033: 5, AR089: 4, AR052: 4, AR060: 4, AR039: 0, AR104: 0 H0616: 3, L0662: 3, L0754: 3, T0039: 2, L0758: 2, S0360: 1, S0045: 1, S6026: 1, S0222: 1, H0427: 1, H0038: 1, L0769: 1, L0805: 1, L0776: 1, L0659: 1, L0779: 1, L0777: 1, L0757: 1 and S0192: 1.	AR033: 8, AR089: 3, 2 AR096: 2, AR104: 2, AR053: 1, AR060: 1, AR061: 1, AR052: 0,
	Met-1 to Phe-10, Gly-13 to Leu-56, Gln-132 to Thr-139.	
	1748	1749
	321 - 737	93 - 410
·	343	344
	805751	806145
	HE9QK23	HNTTB36
	333	334

			64-87					99-130,	13-38, 57-	73, 36-52																
					 			-	· v												. 171					
AR039: 0, AR055: 0	S0346: 1, L0438: 1,	H0520: 1, H0547: 1 and H0519: 1.	AR060: 10, AR055: 7,	AR033: 5, AR096: 4,	AR089: 3, AR061: 3,	AR104: 2, AR053: 2	H0046: 2 and H0616: 1.	AR096: 2, AR039: 1,	AR053: 1, AR089: 1,	AR055: 1, AR060: 1,	AR061: 1, AR033: 1,	AR104: 0, AR052: 0	L0748: 11, L0752: 6,	H0266: 5, L0770: 4, L0740:	4, L0750: 4, L0596: 4,	S0212: 3, L0766: 3, L0803:	3, L0756: 3, H0402: 2,	H0427: 2, S0010: 2, T0003:	2, T0067: 2, S0386: 2,	T0041: 2, L0769: 2, L0796:	2, L0804: 2, H0576: 2,	L0747: 2, H0445: 2, L0588:	2, L0599: 2, H0543: 2,	H0556: 1, S6024: 1, H0341:	1, H0306: 1, H0340: 1,	H0351: 1, S6014: 1, H0431:
								Asn-133 to Trp-143, AR096:	Ala-145 to Phe-151. AR053:																	
	- 		1750		 	-		1751																		
			109 -	462				186 -	674																	
			345		 			346																		
			806385		-			806430																		
			HETJG63					HLDRO45		 -	_															
			335					336	1			_														

		64-85, 24-40, 115- 131, 91- 107, 7-23
		·
1, H0331: 1, T0039: 1, S0280: 1, L0021: 1, H0036: 1, H0390: 1, H0052: 1, H0041: 1, H0123: 1, H0057: 1, H0083: 1, S0023: 1, H0510: 1, S0003: 1, H0628: 1, H0032: 1, H0674: 1, H0598: 1, S0036: 1, H0551:	1, \$0448: 1, L0764: 1, L0648: 1, L0525: 1, L0809: 1, L0519: 1, L0647: 1, L0788: 1, \$0126: 1, H0521: 1, \$0406: 1, \$3012: 1, \$3014: 1, \$0027: 1, L0439: 1, L0779: 1, L0757: 1, L0758: 1, H0444: 1, H0595: 1, H0665: 1, \$0192: 1, H0423: 1, and H0357: 1	AR052: 3, AR033: 3, AR089: 3, AR055: 2, AR096: 2, AR060: 2, AR061: 2, AR039: 2, AR104: 2, AR053: 1 L0439: 5, L0777: 5, H0052: 4, L0803: 4, L0789: 4, L0666: 4, H0556: 3, H0090: 3, L0770: 3, L0766: 3, H0670: 3, L0747: 3, L0756: 3, L0755: 3, S0354:
		1752
		45 - 584
	·	347
		806756
		HFIDZ38
		337

0 01/90304	01/0501/1010
	25-46, 94- 112, 56-72
2, L0768: 2, L0768: 9: 2, 2, L0759: 3: 1, 1, H0661: 6: 1, 1, H0549: 31: 1, 1, L0769: 5: 1, 1, L0647: 5: 1, 1, L0655: 9: 1, 1, L0655: 4: 1, 1, L0752: 1, L0752:	506: 1. 52: 18, 50: 17, 50: 17,
2, S0408: 2, H0580: 2, L0021: 2, H0135: 2, L0768: 2, L0805: 2, L0809: 2, L0787: 2, L0438: 2, H0547: 2, S0406: 2, L0754: 2, L0745: 2, L0758: 2, L0758: 2, S0192: 2, L0758: 2, L0759: 2, S0192: 2, L0758: 2, L0759: 1, H0662: 1, S0356: 1, H0661: 1, H0662: 1, S0358: 1, S0360: 1, H0549: 1, H0268: 1, S0344: 1, L0769: 1, H0268: 1, S0344: 1, L0769: 1, L0774: 1, L0775: 1, L0775: 1, L0775: 1, L0807: 1, L0664: 1, L0807: 1, L0664: 1, L0665: 1, L0665: 1, L0665: 1, L0665: 1, L0665: 1, L0665: 1, L0664: 1, L0740: 1, L0749: 1, L0752: 1, L0740: 1, L0749: 1, L0752: 1, L0731: 1, H0543: 1, L0731: 1, H05	H0423: 1 and H0506: AR089: 28, AR096: 3 AR053: 19, AR052: AR039: 17, AR060: AR033: 14, AR104:
1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	
	Met-1 to Asn-8.
	1753
	113 -
	348
	810257
	HLMD095
	338

MO 01	790304																			•	C I	.70,	301,	104
	192-213			FF 11 77	33-/1, //-	55																		
										<u></u>														
AR055: 11, AR061: 7	AR052: 3, AR055: 3, AR061: 2, AR096: 2,	AK089: 2, AK060: 2, AR033: 1, AR053: 1,	 H0381: 1, H0255: 1,	S0052: 1 and S0028: 1.	AKU55: 8, AKU52: 8,	AR053: 6, AR060: 5,	AR061: 4, AR089: 4,	AR096: 4, AR033: 4,	AR039: 3, AR104: 2	L0439: 6, H0556: 3,	H0052: 2, H0413: 2, L0748:	2, L0754: 2, L0731: 2,	H0543: 2, H0341: 1, S0418:	1, S0442: 1, S0360: 1,	H0734: 1, S0007: 1, S0045:	1, H0393: 1, H0411: 1,	H0545: 1, H0569: 1, H0014:	1, H0271: 1, H0416: 1,	H0286: 1, H0130: 1, H0649:	1, H0529: 1, L0523: 1,	L0438: 1, H0547: 1, H0593:	1, H0435: 1, S0380: 1,	L0741: 1, L0744: 1, L0740:	1, L0749: 1, S0434: 1,
	Leu-28 to Arg-33, Glu-44 to Thr-49,	I yr-66 to Arg-/2,. Pro-82 to Ile-103.		C7 F . 120 10	Gin-35 to Leu-40.																			
	1754				1755																			
	5 - 859				38 - 355																			
	349				320			•																
	810406			23,000	810461																			
	HSLGA19				HGBGM53						•	· · · · · · · · · · · · · · · · · · ·												
	339			,	340																			

	151-168, 61-77	181-199
S0436: 1, L0366: 1, H0423: 1 and S0456: 1.	AR096: 6, AR053: 6, AR052: 5, AR089: 3, AR055: 3, AR104: 2, AR060: 2, AR039: 1 L0748: 6, L0666: 3, L0749: 3, S0420: 2, H0486: 2, L0809: 2, L0789: 2, L0438: 2, H0521: 2, H0713: 1, H0716: 1, S0212: 1, S0300: 1, H0575: 1, H0253: 1, H0319: 1, H0412: 1, H0059: 1, H0100: 1, L0769: 1, L074: 1, L0805: 1, L077: 1,	AR053: 2, AR055: 2, AR033: 1, AR096: 1, AR061: 1, AR104: 1, AR060: 1, AR039: 1,
		Ser-34 to His-42, Pro-51 to Asp-63.
	1756	1757
	3 - 1100	183 -
	351	352
	810586	810899
	HIBCO73	HDPOM13
	341	342

		
	81-97	126-144
	203800, 602404	
	2p13	
AR089: 0, AR052: 0 H0521: 8, H0522: 3, H0644: 2, L0769: 2, L0779: 2, H0580: 1, H0549: 1, S0002: 1 and L0791: 1.	5, 1, 1, 0438:	AR055: 7, AR033: 5, AR096: 5, AR060: 5, AR104: 4, AR061: 3, AR089: 3, AR053: 3, AR052: 2, AR039: 0 H0144: 6, L0803: 4, L0439: 4, L0749: 3, H0421: 2, H0052: 2, L0769: 2, L0774: 2, L0769: 2, L0777: 2, L0731: 2, L0757: 2, L0731: 2, L0757: 1, H0424: 1, H0674: 1, L0021: 1, S0049: 1, H0327: 1, H0424: 1, H0674: 1, L0455: 1, L0456: 1, S0002: 1, L0763: 1, L0761: 1, L0642: 1, L0643: 1,
	Asn-20 to Arg-26, Pro-74 to Glu-79.	Leu-27 to Gln-34, Ser-48 to Ile-56, Lys-73 to Ser-86.
	1758	1759
	171 - 671	54 - 575
	353	354
	811268	812221
	HMEJR75	ноесе93
	343	34

10 01/20004		
	84-111, 39-57	125-156, 27-46, 100-123
L0775: 1, L0793: 1, L0666: 1, H0693: 1, L0352: 1, S0126: 1, S0037: 1, L0742: 1, L0750: 1, L0759: 1 and L0361: 1.	AR055: 12, AR052: 10, AR033: 9, AR060: 7, AR053: 7, AR061: 6, AR096: 6, AR089: 5, AR039: 3, AR104: 3 H0617: 4, H0024: 1, S0028: 1 and L0759: 1.	AR055: 9, AR060: 7, AR033: 6, AR061: 6, AR089: 5, AR053: 5, AR052: 5, AR096: 4, AR039: 3, AR104: 3 H0717: 2, H0589: 2, S0444: 2, S0386: 2, L3905: 2, H0521: 2, S0356: 1, H0549: 1, H0575: 1, S0010: 1, T0010: 1, H0031: 1, H0553: 1, H0135: 1, H0090: 1, H0553: 1, L0521: 1, L0662: 1, L0803: 1, L0775: 1, L0663: 1, S0428: 1, H0144: 1, H0519: 1, H0522: 1,
LO 11,1 80 11,1	Thr-3 to Ser-16, AR His-30 to Asp-35, AR Thr-130 to Leu-135. AR AR AR	Cys-20 to Pro-29, AR Glu-46 to Asp-52, AR Asp-59 to Ser-73. AR AR HU
	1760	1761
	22 - 444	67 - 552
	355	356
	812445	812465
	HLHGA65	HMABF89
	345	346

	171-200, 4-24	105-122	477-500, 385-401, 448-464, 13-29, 514-530, 581-597, 166-182
	120550, 120570, 120575, 153454, 236250, 256700		
	1p36.3		
H0136: 1.	AR060: 1, AR055: 1, AR096: 0, AR061: 0, AR039: 0, AR104: 0, AR033: 0, AR089: 0, AR052: 0, AR053: 0 H0542: 2, H0584: 1, H0611: 1, H0592: 1, H0427: 1, L0644: 1, L0648: 1, L0806: 1, H0522: 1, H0543: 1 and H0422: 1.	AR053: 11, AR096: 9, AR052: 9, AR039: 6, AR089: 4, AR033: 4, AR055: 3, AR060: 3, AR104: 3, AR061: 2 H0656: 2, H0457: 2, H0634: 2, H0521: 2, H0436: 2, H0341: 1, S0418: 1, H0486: 1, H0581: 1, H0271: 1, L0362: 1 and H0423: 1.	AR033: 10, AR104: 9, AR055: 8, AR052: 8, AR060: 8, AR089: 6, AR096: 6, AR053: 5, AR061: 3, AR039: 3 S0222: 8, L0662: 8, L0005: 7, L0665: 7, L0659: 6, L0666: 6, H0547: 6,
	1762 Gly-25 to Gly-30, Pro-105 to Val-112, Glu-137 to Cys-146, Pro-215 to Cys-223, Pro-226 to Arg-240.	1763 Met-1 to Cys-8.	1764 Pro-46 to Tyr-51.
	1762	1763	1764
	195 - 932	311 - 766	74 - 1915
	357	358	359
	812760	813300	815417
	HLKDC74	348 HDTAV81	HETIZ34
	347	348	349

																												•	
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)483:		194:)663:		0777:		354:		0471:		0440:)768:)565:		.0672:		0031:		170:		0212:	-	046:		.0602:	
L0740: 6, S6028: 4, L0483:	4, L0438: 4, L0754: 4,	L0756: 4, L0779: 4, S0194:	S0049: 3, S0388: 3,	L0646: 3, L0521: 3, L0663:	1, L0664: 3, H0435: 3,	H0696: 3, L0439: 3, L0777:	3, H0624: 2, H0171: 2,	S0356: 2, S0442: 2, S0354:	S0360: 2, S0408: 2,	H0046: 2, H0563: 2, L0471:	2, S0051: 2, H0266: 2,	H0040: 2, H0623: 2, S0440:	L0598: 2, L0520: 2,	.0641: 2, L0771: 2, L0768:	2, L0774: 2, L0805: 2,	776: 2, L0518: 2, L0	2, H0519: 2, H0670: 2,	H0660: 2, H0648: 2, H0672:	2, S0028: 2, L0751: 2,	731: 2, L0758: 2, S(2, L0596: 2, L0595: 2,	026: 2, S0196: 2, H(1, H0686: 1, H0685: 1,	H0717: 1, H0381: 1, S0212:	1, H0662: 1, S0418: 1,	S0376: 1, S0045: 1, S0046:	1, H0411: 1, H0369: 1	H0550: 1, H0438: 1, H0602:	1, T0040: 1, H0013: 1,
ITO.	4.	<u>C</u>	<u>4</u>	<u>2</u>	3, 1	OH HO	3,]	<u> SO:</u>	2,5	OH OH	<u> </u>	HO	2,1	07	2,	<u>[L0]</u>	2,7	OH	, ,	LO	2,7	<u>80</u> 0	1,1	OH HO	1,1	SO:	1,1	HO	1,]
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H0427: 1, 50280. 1, H0590. H0427: 1, 20280. 1, 30474. 1, H0428: 1, H0428: 1, H0428: 1, H023: 1, L023: 1,
HWLIX39 815669 360 84- 1765 Ser-4 to Glu-11, AR039: 13, S0438: 1, HWLIX39 815669 360 84- 1765 Ser-4 to Glu-11, AR039: 13, S0408: 1, S039:
HWLIX39 815669 360 84- 1765 Ser-4 to Glu-11, AR039: 13, S0438: 1, HWLIX39 815669 360 84- 1765 Ser-4 to Glu-11, AR039: 13, S0408: 1, S039:
HWLIX39 815669 360 84- 1765 Ser-4 to Glu-11, AR039: 13, S0438: 1, HWLIX39 815669 360 84- 1765 Ser-4 to Glu-11, AR039: 13, S0408: 1, S039:
HWLIX39 815669 360 84- 1765 Ser-4 to Glu-11, 1052 Tyr-14 to Lys-29, Arg-101 to Arg-106, Gly-239 to Tyr-246.
HWLIX39 815669 360 84- 1765 Ser-4 to Glu-11, 1052 Tyr-14 to Lys-29, Arg-101 to Arg-106, Gly-239 to Tyr-246.
HWLK39 815669 360 84 - 1765
HWLIX39 815669 360 84 -
HWLIX39 815669 360
HWLIX39 815669
HWLIX39

	The state of the s
	68-93, 39-
	65
	107280, 107280, 107400, 107400, 122500, 245200, 601841
	14q32.1
1, H0586: 1, H0253: 1, H0039: 1, H0038: 1 and S0434: 1.	AR089: 5, AR060: 3, AR089: 3, AR089: 1, AR052: 1, AR039: 1, AR052: 1, AR061: 1, AR052: 1, AR061: 1, AR053: 0, AR104: 0, AR053: 0, AR104: 0, AR053: 5, L0758: 3, H0370: 2, H0107: 2, L0779: 2, H0521: 2, L0747: 2, L0779: 2, H0521: 2, L0747: 1, S0360: 1, S0442: 1, S0358: 1, H0580: 1, H0486: 1, H0659: 1, H0633: 1, H0488: 1, H0659: 1, L0770: 1, L0769: 1, L0769: 1, L0648: 1, L0769: 1, L0769: 1, L0770: 1, L0748: 1, L0777: 1, L0748: 1, L0777: 1, L0755: 1, S0434: 1, S0436: 1, L0548: 1, L0553: 1, L0601: 1, H0216: 1 and H0543: 1.
	1766 Pro-14 to Gly-23, Arg-93 to Pro-100.
	1766
	37 - 354
	361
	823632
	HDTJT12
	351

44-64	39-64, 57-79, 89-114	39-73	53-70, 7-
		581: 1.	
AR055: 7, AR052: 4, AR060: 4, AR061: 4, AR039: 4, AR053: 4, AR033: 3, AR096: 3, AR089: 2, AR104: 1 H0309: 1	AR039: 54, AR096: 22, AR033: 21, AR053: 21, AR055: 17, AR104: 15, AR089: 13, AR060: 12, AR052: 11, AR061: 9 S0474: 5, L0770: 3, L0790: 3, H0421: 2, S0422: 2, L0769: 2, L0759: 2, H0327: 1, H0566: 1, H0051: 1, S0036: 1, L3905: 1, L0803: 1, L0809: 1 and S0260: 1.	AR089: 5, AR060: 5, AR061: 5, AR096: 3, AR055: 3, AR033: 2, AR104: 2, AR039: 2, AR053: 1, AR052: 1 S0046: 1, H0592: 1, H0486: 1, H0013: 1, H0581: 1, L0809: 1 and H0144: 1.	AR039: 14, AR096: 13, AR089: 12, AR060: 10, AR104: 10, AR033: 8,
1767 Glu-14 to Met-26, Leu-77 to Asn-88, Lys-96 to Gly-104.	Ala-4 to Glu-13, Gln-80 to Trp-90.	Met-1 to Glu-6, Ser-16 to Phe-40, Glu-75 to Leu-83, Cys-86 to Lys-99, Ser-116 to Asp-124, Leu-127 to Glu-136.	Ser-42 to Ser-47, Arg-91 to Lys-99.
1767	1768	1769	1770
117 - 455	91 - 459	309 - 776	261 - 653
362	363	364	365
824800	825910	827237	827837
352 HSVCA10 824800	HDFQA53	HE9PC92	HMSOU92
352	353	354	355

	93-109	97-124
	120550, 120570, 120575, 130500, 133200, 600975	
	1p36.33- 1p36.11	
AR052: 7, AR053: 6, AR055: 5, AR061: 4 S0426: 2 and L0596: 2.	AR061: 6, AR033: 5, AR055: 5, AR060: 4, AR104: 3, AR052: 3, AR053: 3, AR089: 2, AR096: 2, AR039: 0 L0415: 1, H0619: 1, H0013: 1, H0052: 1, T0010: 1, H0591: 1, H0521: 1, S3014: 1, L0439: 1, L0596: 1 and S0242: 1.	AR096: 2, AR061: 1, AR033: 1, AR060: 1, AR053: 0, AR104: 0, AR039: 0, AR089: 0, AR055: 0 L0754: 15, L0439: 14, L0666: 7, L0777: 7, S0003: 6, L0163: 4, H0553: 4, H0040: 4, L0803: 4, L0779: 4, L0755: 4, H0624: 3, S0358: 3, L0471: 3, S0426: 3, L0794: 3, L0659: 3, H0547: 3, L0602: 3, H0696: 3, L0748: 3, L0731: 3, L0757: 3, H0295: 2, S0212: 2, H0661: 2, S0376: 2,
	Cys-29 to Asp-35, Pro-63 to Pro-70.	Arg-16 to Glu-27, Gln-37 to Phe-44, Cys-52 to Glu-58, Leu-85 to Lys-91.
	1771	1772
	122 - 457	115 - 489
	366	367
	828103	828170
	HE8OX52	HDAAS81
	356	357

																							-					
43	4.			_					<u></u>				e:				.;				3:		<u></u>				<u></u>	
H0329: 2, S0046: 2, S0132: 2, L0717: 2, H0581: 2,	H0023: 2, H0428: 2, H0644:	2, L0662: 2, L0776: 2,	L0663: 2, S0374: 2, L0438:	I0555: 2, L0744: 2,	.0747: 2, S0434: 2, S0242:	2, S0194: 2, S0276: 2,	S0196: 2, H0686: 1, S0040:	'0049: 1, H0583: 1,	S0282: 1, H0255: 1, H0638:	1, S0442: 1, S0444: 1,	60: 1, H0645: 1, H035	0278: 1, H0497: 1,	H0333: 1, H0632: 1, H0486:	1, H0013: 1, H0108: 1,	H0042: 1, H0575: 1, H0004:	l, H0251: 1, H0263: 1,	H0046: 1, H0457: 1, H0024:	l, H0014: 1, H0179: 1,	S0214: 1, H0328: 1, L0194:	1, H0628: 1, H0090: 1,	H0551: 1, T0067: 1, H0623:	.0564: 1, H0633: 1,	S0142: 1, H0529: 1, L0369:	1, L0763: 1, L0770: 1,	'61: 1, L0372: 1, L0646	1, L0764: 1, L0648: 1,	L0768: 1, L0766: 1, L0774:	, L0375: 1, L0651: 1,
H03)OH	2,1	907	2, H	L07	2, S	S01	1,T	S02	1, S	S03	1, S	H03	1, H)OH	1, H)OH	1, H	S02	1, H	HOS	1, L	S01	1, L	L07	1, L	107	1, L
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	40-71, 83-99, 32-48
0519: 0519: 0152: 0758: and	7, 14, 14, 17, 17, 17, 17, 17, 17, 17, 17, 17, 17
0653: 1, LC L0665: 1, H .0565: 1, H .0682: 1, SC .0330: 1, SC .0750: 1, LC .0750: 1, LC .0591: 1, SC .0591: 1, SC	8, AR053: 7, AR055: 3, AR060: 4, AR060: 23, AR104: 215, L0775: 9, L0770: 7, L0777: 4, L0601: 4, H0772: 3, L0752: 3, L0787: 2, L0787: 1, H0685: 1, H0685: 1, H0687: 1,
L0805: 1, L0653: 1, L0657: 1, L0789: 1, L0665: 1, H0144: 1, L0565: 1, H0519: 1, H0689: 1, H0682: 1, H0672: 1, S0330: 1, S0152: 1, H0521: 1, H0704: 1, S0260: 1, H0595: 1, S0436: 1, L0591: 1, S0436: 1, L0591: 1, S0436: 1, H0667: 1, S0192: 1 and H0506: 1.	AR052: 8, AR053: 7, AR033: 7, AR055: 5, AR089: 4, AR060: 4, AR096: 3, AR061: 3, AR039: 3, AR104: 2 L0779: 15, L0775: 9, L0758: 9, L0770: 7, L0769: 6, L0740: 5, L0754: 5, L0757: 5, S0408: 4, L0766: 4, L0789: 4, L0777: 4, L0759: 4, L0601: 4, H0224: 3, L0771: 3, L0776: 3, L0747: 3, L0752: 3, L0755: 3, H0549: 2, H0196: 2, H0083: 2, S0150: 2, L0763: 2, L0764: 2, L0787: 2, H0660: 2, L0750: 2, L0780: 2, H0170: 1, H0685: 1, S0040: 1, H0657: 1, H0638:
	Gly-71 to Leu-84.
	m
	142 - 177
	368
	828267
	HUSIK57
	358

	193-209, 152-168, 117-133
	·
1, S0418: 1, S0356: 1, S0358: 1, H0329: 1, S0278: 1, H0550: 1, S0222: 1, H0586: 1, L0622: 1, L0021: 1, H0390: 1, L0471: 1, S0050: 1, H0014: 1, H0594: 1, H0266: 1, H0188: 1, H0615: 1, H0618: 1, H0615: 1, H0560: 1, S0144: 1, L0772: 1, L0646: 1, L0774: 1, L0653: 1, L0655: 1, L0774: 1, L0538: 1, H0520: 1, L078: 1, L0515: 1, L0526: 1, L0783: 1, L0546: 1, H0648: 1, S0152: 1, S0190: 1, L0742: 1, L0746: 1, L0756: 1, H0542: 1 and H0352: 1.	
	Asp-50 to Ile-64, Gln-66 to Asp-71, Thr-177 to Ser-183, Arg-246 to Thr-263.
	1774
	903
	369
	828597
	HPRBB67
	359

	91-108	227-258
L0777: 2, H0265: 1, H0305: 1, S0356: 1, H0013: 1, H0318: 1, H0052: 1, H0309: 1, H0597: 1, L0471: 1, H0032: 1, L0455: 1, L0638: 1, L0768: 1, L0775: 1, L0651: 1, L0809: 1, L0788: 1, S0053: 1, S0216: 1, H0144: 1, S0328: 1, H0521: 1, H0478: 1, L0780: 1 and L0608: 1.	AR055: 10, AR061: 9, AR060: 6, AR033: 5, AR052: 5, AR089: 4, AR053: 3, AR039: 2, AR096: 1, AR104: 1 H0583: 1, H0415: 1 and S0150: 1.	AR033: 15, AR039: 13, AR055: 13, AR053: 12, AR096: 11, AR089: 11, AR052: 11, AR061: 10, AR104: 9, AR060: 8 L0770: 4, L0748: 3, L0750: 3, H0622: 2, H0169: 2, L0769: 2, L0766: 2, L0775: 2, L0806: 2, L0776: 2, H0436: 2, L0741: 2,
	Glu-42 to Ser-53.	
	1775	
	617	143 - 919
	370	371
	828682	828777
·	HPIBM51	HLYFY81
	360	361

	1	
	83-109	305-321
		120950, 120960, 130500, 133200,
		1p32-p34
L0740: 2, H0445: 2, H0556: 1, S0114: 1, H0657: 1, S0001: 1, H0255: 1, H0638: 1, S0444: 1, S0046: 1, H0545: 1, H0530: 1, H0546: 1, H0545: 1, H0651: 1, H0651: 1, H0654: 1, H0652: 1, L0773: 1, L0772: 1, L0773: 1, L0662: 1, L0783: 1, L0665: 1, S0152: 1, S3012: 1, L0777: 1, L0758: 1 and H0506: 1	AR104: 2, AR039: 1, AR096: 1, AR033: 1, AR055: 1, AR060: 1, AR061: 0, AR089: 0, AR053: 0, AR052: 0 S0002: 2, H0431: 1, S0003: 1, H0644: 1, H0521: 1, S0044: 1, S0146: 1 and S0028: 1.	AR053: 81, AR052: 72, AR033: 37, AR089: 34, AR096: 20, AR055: 14, AR060: 12, AR039: 11,
	Glu-22 to Lys-27, Glu-39 to Asn-44, Met-55 to Ser-60, Leu-71 to Gln-80.	Met-1 to Ser-9.
	1777	1778
·	398 - 730	174 - 1403
	372	373
	828826	828922
	362 HDPLO68	ннепи25

	81-99
138140, 168360, 171760, 171760, 176100, 176100, 178300, 187040, 255800, 600101, 600650, 600650, 600722, 600722,	
AR104: 9, AR061: 9 H0046: 6, L0794: 4, H0547: 4, L0439: 3, L0779: 3, H0543: 3, L0454: 2, L0768: 2, L0663: 2, L0665: 2, L0749: 2, L0777: 2, H0716: 1, H0657: 1, H0662: 1, S0278: 1, T0039: 1, H0013: 1, H0052: 1, L0471: 1, H0591: 1, H0264: 1, S0440: 1, S0150: 1, S0002: 1, L0369: 1, L0640: 1, L0770: 1, L0662: 1, L0766: 1, L0803: 1, L0804: 1, L0378: 1, L0806: 1, L0666: 1, H0519: 1, H0539: 1, H0521: 1, S0176: 1, H0555: 1, L0731: 1, L0758: 1, L0362: 1 and S0424: 1,	AR096: 2, AR089: 2, AR033: 1, AR039: 1, AR061: 1, AR052: 1, AR060: 1, AR055: 0, AR053: 0, AR104: 0 S0414: 8, L0754: 7, L0766: 6, L0758: 5, L0794: 3, L0592: 3, S0007: 2, L0471: 2, H0032: 2, H0038: 2, L0659: 2, H0710: 2,
AR104 H0047: 3, H0547: 2, L0748: 1, S027 H0013: 1, H055 L0770: 1, L086 L0378: 1, H051: 1, L074: 1, L074: 1, L074: 1, L074: 1, L074: 1, L074: 1, L074:	Gly-101 to Tyr-110. AR036: AR033: AR061: AR066: AR053: S0414: L0766: 6 3, L0592 L0471: 2 2, L0659
. 0	-522 1779 Gly-10
	828926 374 49 -
·	HNTBH70
	364

WO 01/90304	1 C 1/0501/10450
	15-31, 172-190
L0745: 2, L0756: 2, H0624: 1, H0171: 1, S0278: 1, H0389: 1, H0431: 1, H0632: 1, H0156: 1, L0157: 1, H0510: 1, H0416: 1, S0336: 1, S0003: 1, H0428: 1, H0553: 1, H0169: 1, H0212: 1, H0040: 1, H0634: 1, L0638: 1, L0662: 1, L0803: 1, L0804: 1, L0650: 1, L0774: 1, L0776: 1, L0655: 1, L0809: 1, L0791: 1, S0052: 1, H0519: 1, L0355: 1, H0696: 1, H0436: 1, H0478: 1, L0779: 1, L0755:	AR061: 3, AR033: 2, AR061: 3, AR033: 2, AR089: 2, AR060: 2, AR096: 1, AR052: 1, AR055: 1, AR104: 1, AR053: 1, AR104: 1, AR053: 1, AR039: 0 S0414: 26, L0777: 8, L0758: 8, L0439: 5, L0779: 5, L0752: 4, L0471: 3, H0266: 3, H0032: 3, S0422: 3, L0766: 3, L0803: 3, L0809: 3, S0380: 3, L0740: 3, L0731: 3, S0192: 3, H0170: 2, H0657: 2, S0358: 2, S6016: 2, H0574: 2,
	Asp-42 to Lys-57.
	1780
	55 - 1137
	375
	828988
	HMIAN37
	365

			_																										
						-					-																		
																												-	
2, H0051:	: 2,	, L0653:	. 2,	2, L0745:	: 2,	, S0412:	§: 1,	, H0728:	: 1,	, H0392:	7: 1,	, H0309:	. 1,	l, S0022:	3: 1,	l, H0212:	1,	l, T0069:	: 1,	1, L0637:	: 1,	, L0804:	: 1,	, L0636:		, S0374:	: 1,	, H0518:	: 1,
H0052: 2, H0009: 2, H0051:	2, S6028: 2, H0090: 2,	H0591: 2, S0440: 2, L0653:	2, L0666: 2, L0663: 2,	H0689: 2, H0658: 2, L0745:	2, L0747: 2, L0750: 2,	.0753: 2, H0423: 2, S0412:	2, H0171: 1, H0656: 1,	S0360: 1, S0408: 1, H0728:	1, H0351	H0411: 1, S0222: 1, H0392:	l, H0455: 1, H0587: 1,	F0114: 1, S0474: 1, H0309:	1, H0263: 1, H0596: 1,	H0046: 1, H0083: 1, S0022:	l, H0615: 1, H0428: 1,	H0553: 1, H0628: 1, H0212:	l, H0068: 1, S0036: 1	, H0623: 1	1, H0494: 1, S0438: 1,	H0633: 1, H0529: 1, L0637:	1, L0771	L0794: 1, L0388: 1, L0804:	1, L0805	L0607: 1, L0659: 1, L0636:	1, L0790	L0665: 1	1, L0438: 1, H0519: 1,	S0328: 1, S0378: 1, H0518:	1, S0152: 1, H0521: 1,
H0052: 2	2, \$6028:	H0591: 2	2 , L0666:	H0689: 2	2, L0747:	L0753: 2,	2, H0171:	S0360: 1,	1, L0717:	H0411: 1	1, H0455	T0114: 1,	1, H0263	H0046: 1	1, H0615	H0553: 1	1, H0068	H0268: 1	1, H0494	H0633: 1	1, L0764:	L0794: 1,	1, L0774:	L0607: 1,	1. L0647:	L0664: 1,	1, L0438:	S0328: 1,	1, S0152:
	<u> </u>										<u>.</u>												_						
				•										 .											_				

Т	
	141-158, 1-17, 102- 118
H0696: 1, S3012: 1, L0742: 1, L0756: 1, L0759: 1, H0445: 1, S0434: 1, L0581: 1, S0011: 1, H0653: 1, H0667: 1, S0242: 1, H0422: 1 and S0042: 1.	AR033: 72, AR055: 60, AR089: 41, AR052: 40, AR053: 38, AR060: 37, AR061: 25, AR096: 11, AR104: 6, AR039: 4 L0777: 15, L0766: 7, L0776: 6, L0751: 6, L0770: 4, L0775: 4, L0806: 4, L0805: 4, L0780: 4, S0214: 3, L0769: 3, L0774: 3, L0755: 3, H0599: 2, S0003: 2, L0768: 2, L0778: 2, L0756: 2, L0779: 2, L0756: 2, L0779: 2, L0752: 2, L0758: 2, L079: 2, L0603: 2, H0159: 1, H0661: 1, S0045: 1, S0222: 1, L0586: 1, H0575: 1, S0010: 1, S0474: 1, H0309: 1, S0050: 1, S0051: 1, S0052: 1, H0553: 1, H0169: 1, H0591: 1, H0038: 1, H0634: 1, S0142: 1, S0422: 1,
10696: 1, S3012: 1, I 1, L0756: 1, L0759: 1 10445: 1, S0434: 1, I 1, S0011: 1, H0653: 1 10667: 1, S0242: 1, I and S0042: 1.	AR033: 72, AR055: 60, AR089: 41, AR052: 40, AR053: 38, AR060: 37, AR061: 25, AR096: 11, AR104: 6, AR039: 4 L0777: 15, L0766: 7, L0777: 15, L0766: 7, L0775: 4, L0806: 4, L0775: 4, L0806: 4, L0755: 3, H0599: 2, S0003; L0755: 3, H0599: 2, L0743; L0756: 2, L0768: 2, L0778: 2, L0756: 2, L0779: 2, L0756: 2, L0754: 2, L0758: 2, L0754: 2, L0756: 2, L0758: 2, L0759: 2, L0756: 1, S0045: 1, S0045: 1, S0045: 1, S0045: 1, S0050: 1, S0050: 1, H0653: 1, S0042: 1, S0142: 1, S01
H0696: 1, L075 H0445: 1, S001 H0667: 1 and S(AR033: AR089: AR061: AR104: L0777: L0777: L0776: 4, L0776: 2, L076: 2, L076: 2, L076: 2, L076: 2, L078: 1, S004: 1, S047: S0050: 1, H055 H0591: 1, S014;
	1781
;	83 - 862
	376
	829071
	HPFD125
	366

VO 01/90304	PC1/USU1/1043
	88-106
	107470, 107470, 107470, 120110, 121014, 164200, 601316, 601666, 601757, 602772
	6q21-q23.2
L0369: 1, L0771: 1, L0521: 1, L0655: 1, L0783: 1, L0787: 1, S0374: 1, H0659: 1, S0152: 1, S3012: 1, L0439: 1, L0747: 1, L0750: 1, S0026: 1 and H0543: 1.	AR053: 2, AR052: 2, AR096: 2, AR089: 2, AR033: 1, AR104: 1, AR055: 1, AR104: 1, AR055: 1, AR059: 1, AR060: 1, AR061: 1 L0740: 12, L0439: 10, L0766: 7, L0769: 4, L0794: 4, L0756: 4, H0549: 3, L0768: 3, L0769: 3, L0768: 3, L0760: 2, H0423: 3, S0007: 2, S0036: 3, L0769: 2, H0327: 2, H0052: 2, L0763: 2, L0770: 2, H0144: 2, L0758: 2, H0556: 1, L0760: 1, S6026: 1, S0300: 1, H0550: 1, H0331: 1, H0194: 1, H0103: 1, H0103
	Met-1 to Asn-12, Glu-17 to Gln-26, Thr-43 to Ser-70, Ala-72 to Lys-88, Asp-131 to Val-136, Val-183 to Asp-190, Pro-192 to Ala-203.
	1782
	282 - 938
	377
	829308
	HIBCN93
	367

·	98-69
	120950, 120960, 138140, 178300, 180069, 180069, 187040, 201450, 248610, 600101, 600650, 600650, 600622,
	1p32-p31
H0124: 1, H0068: 1, S0036: 1, H0135: 1, H0038: 1, H0616: 1, H0551: 1, T0067: 1, H0100: 1, H0560: 1, L0649: 1, L074: 1, L074: 1, L0517: 1, L0809: 1, L0647: 1, L0789: 1, L0792: 1, L0352: 1, S0126: 1, H0518: 1, S0044: 1, S0044: 1, L0747: 1, L0686: 1, L0592: 1, S0196: 1 and H0352: 1.	Asp-9 to Tyr-15, AR089: 23, AR096: 19, Pro-27 to Lys-48, AR052: 18, AR039: 15, Ser-61 to Asn-67, AR053: 15, AR033: 14, Asp-104 to Asn-113. AR060: 9, AR055: 8, AR061: 7, AR104: 6 L0748: 10, L0776: 9, L0777: 9, L0776: 7, L0749: 7, L0777: 9, L0776: 7, L0747: 5, H0009: 4, S0036: 4, S0210: 4, L0779: 4, L0439: 4, L0779: 4, L0752: 4, S0116: 3, S0045: 3, H0581: 3, H00581: 3, H0059: 3, L0770: 3, L0805: 3, L0740: 3,
	1783 F 8 1 1783
	14 - 457
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	829463
	нсирм68
	368

WO 01/90304 PCT/US01/16450

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L0755: 3, L0731: 3, L0758:	3, £0239. 3, 30412. 3, 80410: 2. H0645: 2. H0369:	2, S0222: 2, H0497: 2,	H0013: 2, H0251: 2, H0083:	2, H0615: 2, S0422: 2,	.0631: 2, L0764: 2, L0803:	2, L0774: 2, L0775: 2,	: 2, L0659: 2, H0519:	2, H0711: 2, H0670: 2,	H0539: 2, S0350: 2, H0436:	2, L0745: 2, L0750: 2,	.0362: 2, L0600: 2, H0624:	, H0171: 1, H0265: 1,	H0556: 1, T0002: 1, H0717:	l, S6024: 1, T0049: 1,	H0583: 1, H0650: 1, S0001:	, H0662: 1, H0402: 1,	H0638: 1, S0356: 1, S0376:	, S0360: 1, H0329: 1,	H0729: 1, H0728: 1, L0717:	, H0351: 1, H0441: 1,	H0455: 1, H0592: 1, H0586:	l, H0492: 1, H0485: 1,	F0040: 1, H0244: 1, H0427:	l, L0022: 1, H0004: 1,	S0010: 1, S0346: 1, T0048:	l, H0052: 1, H0596: 1,	H0597: 1, H0046: 1, H0050:	1, L0471: 1, H0024: 1,
L0755	S0410	2, S02	H0013	2, H06	L0631	2, L07	L0527	2, H07	H0539	2, L07	L0362	1, H01	H0556	1, S60	H0583	1, H06	H0638	1, S03	H0729	1, H03	H0455	1, H04	T0040	1, LOO	S0010:	1, H00	H0597	1, L04
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	108-137, 137-168
	131400, 147061, 147575, 147575, 147575,
	5q31.1
H0051: 1, S6028: 1, S0003: 1, H0428: 1, T0023: 1, L0483: 1, H0169: 1, L0456: 1, H0169: 1, L0456: 1, H0163: 1, H0169: 1, H0038: 1, H0040: 1, T0067: 1, H0268: 1, T0041: 1, H0494: 1, H0561: 1, H0646: 1, S0208: 1, S0002: 1, S0426: 1, H0743: 1, H0529: 1, L0520: 1, L073: 1, L0800: 1, L053: 1, L0519: 1, L0783: 1, L0809: 1, L0791: 1, L0668: 1, L0663: 1, H0659: 1, H0659: 1, H0659: 1, H0659: 1, H0644: 1, S0434: 1, L0596: 1, H0668: 1, L0661: 1, H0668: 1, L0667: 1, H0668: 1, H0667: 1, H0668: 1, H0667: 1, L0596: 1, H0667: 1, L0596: 1, H0668: 1, H0667: 1, L0596: 1, H0668: 1, H0667: 1, L0596: 1, H0668: 1, H0667: 1, S0194: 1, H0643: 1 and: 1.	AR039: 4, AR053: 3, AR089: 3, AR033: 3, AR055: 3, AR096: 2, AR060: 2, AR061: 2, AR104: 1, AR052: 0
	Asp-37 to Tyr-46, Asn-48 to Gly-55, Ala-58 to Gly-65, Thr-68 to Trp-81, Ser-89 to Thr-101,
·	1784
	830 - 279
	379
	829601
	HCFCU33
	369

VO 01/90304	FC1/US01/10450
	258-274, 217-233, 182-198
153455, 159000, 181460, 600807, 601596, 602089	
.:	\$ \$ E ::
H0545: 2, H0135: 2, S0342: 1, H0484: 1, S0358: 1, S0278: 1, H0550: 1, H0370: 1, H0574: 1, H0492: 1, H0599: 1, H0575: 1, H0546: 1, H0123: 1, H0050: 1, H0012: 1, H0620: 1, S0051: 1, H0100: 1, H0494: 1, S0352: 1, H0132: 1, H0130: 1, L0764: 1, L0766: 1, H0696: 1, S3014: 1, L0748: 1, L0745: 1, L0756: 1, L0731: 1, H0445: 1, L0595: 1, S0196: 1 and	AR055: 8, AR052: 7, AR096: 5, AR089: 5, AR033: 5, AR060: 5, AR104: 3, AR039: 2 L0748: 10, L0740: 8, L0754: 7, L0770: 5, H0539: 5, L0439: 5, L0362: 5, H0641: 4, L0777: 4, L0599: 4, L0603: 4, S0444: 3, H0486: 3, L0804: 3, H0547: 3, L0749: 3, L0750: 3, H0663: 2, S0360: 2, S0045:
Leu-105 to Arg-110. H0545: 2, H0135: 2, S0342: 1, H0484: 1, S 1, S0278: 1, H0484: 1, S 1, S0278: 1, H0550: 1 H0370: 1, H0574: 1, I, H0599: 1, H0575: H0546: 1, H0123: 1, I, H0012: 1, H0620: 1, S0051: 1, H0100: 1, H0130: 1, H0130: 1, H0144: 1, H0519: S0126: 1, H0670: 1, H1, H0696: 1, S3014: 1, H0696: 1, S3014: 1, H0696: 1, S3014: 1, H0696: 1, S0196: 1 at H0422: 1, H06422: 1	Arg-5 to Ser-10, Ser-29 to Ser-39, Tyr-99 to Asp-104, Asp-115 to Ile-129, Gln-131 to Asp-136, Ser-208 to Ser-215, Lys-236 to Glu-247, Ser-307 to Ser-316, His-325 to Asn-331. His-325 to Asn-331.
	1785
	1391
	380
	829736
	HTGCM10
	370

					•									
33:	21:			, c			51:	50:	38:				ł6:)5:
2, H0438: 2, H0013: 2, H0599: 2, S0003: 2, L0483: 2, H0031: 2, H0591: 2, S0144: 2, L0794: 2, L0803:	2, L0654: 2, L0657: 2, L0809: 2, L0438: 2, H0521: 2, H0522: 2, S3014: 2,	L0751: 2, L0731: 2, L0596: 2, L0593: 2, S0242: 2, H0624: 1, S0040: 1, S0134:	1, H0583: 1, H0657: 1, 50134: 1, H0583: 1, H0657: 1, H0483: 1, H0661: 1, H0662:	1, H0402: 1, H0638: 1, S0420: 1, S0442: 1, H058	1, H0329: 1, H0734: 1, S0072:	1, H0441: 1, H0431: 1,	H0587: 1, S0280: 1, H0251: 1, H0569: 1, H0012: 1,	H0057: 1, H0375: 1, S02 1, H0428: 1, L0142: 1.	H0169: 1, S0036: 1, H0038:	1, H0616: 1, H0412: 1, H0494: 1, H0625: 1, S04	1, S0440: 1, H0509: 1,	S0150: 1, S0344: 1, S0422:	1, 50002: 1, E0705: 1, L0769: 1, L0761: 1, L0646:	1, L0773: 1, L0766: 1, L0774: 1, L0775: 1, L0805:
													-	

	102-118, 54-70
1, L0653: 1, L0776: 1, L0636: 1, L0792: 1, L0666: 1, H0520: 1, H0519: 1, H0593: 1, S0126: 1, H0659: 1, H0658: 1, H0710: 1, H0436: 1, S0027: 1, L0744: 1, L0747: 1, L0780: 1, L0752: 1, L0755: 1, L0758: 1, L0759: 1, S0436: 1, L0591: 1, L0592: 1 and S0276: 1.	AR052: 8, AR096: 7, AR033: 7, AR104: 5, AR053: 5, AR089: 4, AR060: 4, AR055: 4, AR061: 3, AR039: 3 H0556: 11, H0046: 7, H0617: 6, L0750: 6, L0769: 5, L0766: 5, L0759: 5, S0434: 5, H0265: 3, H0584: 3, S0358: 3, S0360: 3, H0266: 3, L0770: 3, L0771: 3, L0439: 3, L0749: 3, H0543: 3, H0657: 2, H0494: 2, S0440: 2, L0763: 2, L0764: 2, L0666: 2, H0144: 2, S0328: 2, S0330: 2, S0406: 2, L0751: 2, L0754:
	Arg-9 to Thr-17, Lys-74 to Arg-89, Arg-135 to Glu-143, Ser-164 to Thr-170.
	1786
	66 - 575
	381
	830029
	HFIIS05
	371

	-					•					-	-																
2, L0747: 2, L0592: 2, S0026: 2, T0002: 1, H0686:	1, H0713: 1, H0294: 1,	T0049: 1, H0341: 1, H0664:	1, H0402: 1,	H0638: 1, S0418: 1, S0408:	1, L0717: 1,	H0392: 1, H0333:	1, H0492: 1, H0486: 1,	T0060: 1, H0069: 1, H0427:	1, H0036: 1,	H0196: 1, H0251:	1, H0545: 1,	L0157: 1, H0012: 1, H0350:	1, T0006: 1,	H0604: 1, H0628: 1, H0181:	1, H0135: 1,	H0413: 1, T0042:	1, H0560: 1, H0359: 1,	H0561: 1, H0529: 1, L0762:	1, L0761: 1, L0372: 1,	L0641: 1, L0648:	1, L0774: 1,	L0806: 1, L0653:	1, H0547: 1,	H0539: 1, H0521: 1, H0555:	1, S0037: 1, S0206: 1,	.0745: 1, L0753: 1, L0755:	1, H0445: 1, S0194: 1 and	
2, L0747: S0026: 2.	1, H0713:	T0049: 1,	1, H0228:	H0638: 1,	1, S0046:	H0370: 1,	1, H0492:	T0060: 1,	1, H0575:	T0001: 1,	1, T0115:	L0157: 1,	1, H0328:	H0604: 1,	1, L0055:	H0616: 1,	1, H0560:	H0561: 1,	1, L0761:	L0646: 1,	1, L0768:	L0775: 1,	1, L0809:	H0539: 1,	1, S0037:	L0745: 1,	1, H0445:	S0276: 1.
			_																									

28-59, 86- 102	76-92, 53- 59	10-30, 41- 57, 171- 187, 194- 210
AR089: 20, AR096: 9, AR052: 8, AR053: 6, AR060: 5, AR033: 4, AR039: 3, AR055: 3, AR104: 3, AR061: 2 S0354: 3, H0050: 1, L0483: 1 and H0670: 1.	AR096: 9, AR104: 9, AR033: 7, AR089: 6, AR039: 5, AR060: 5, AR053: 4, AR052: 3, AR061: 2, AR055: 2 S0374: 2	AR033: 5, AR053: 5, AR052: 4, AR055: 4, AR089: 3, AR061: 2, AR060: 2, AR096: 1, AR104: 0, AR039: 0 H0663: 1, H0586: 1, H0587: 1, H0039: 1, S0440: 1 and L0771: 1.
Lys-4 to Glu-11.		Ile-72 to Asn-77, Asp-98 to Gly-104.
1788	1789	1790
5 - 631	231 - 548	75 - 911
383	384	385
830262	830339	830348
HWLFQ55	HWLBK80	НWНQR45
		375
	HWLFQ55 830262 383 5-631 1788 Lys-4 to Glu-11. AR089: 20, AR096: 9, AR052: 8, AR053: 6, AR060: 5, AR033: 4, AR039: 3, AR055: 3, AR039: 3, AR061: 2 S0354: 3, H0050: 1, L0483: 1 and H0670: 1.	830262 383 5-631 1788 Lys-4 to Glu-11. AR089: 20, AR096: 9, AR052: 8, AR053: 4, AR060: 5, AR033: 4, AR039: 3, AR055: 3, AR104: 3, AR061: 2 S0354: 3, H0050: 1, L0483: 1 and H0670: 1. AR096: 9, AR104: 9, AR039: 5, AR060: 5, AR039: 5, AR052: 3, AR061: 2, AR055: 2 S0374: 2

376-392, 278-294, 246-262
18
Leu-184 to Trp-190, AR060: 13, AR061: 11, Val-208 to Met-217, AR089: 6, AR033: 5, Glu-221 to Thr-228, AR104: 4, AR053: 4, Val-238 to Gly-243, AR096: 3, AR039: 3, Asp-266 to Asn-272, AR055: 2, AR052: 2 Arg-370 to Lys-375. L0803: 30, S0358: 13, S0360: 6, S0438: 6, L0794: 6, L0777: 5, S0408: 5, S0440: 5, L0777: 5, S0408: 5, S0440: 4, L0777: 5, S0444: 4, H0510: 4, L0439: 4, L0777: 4, L0601: 4, S0026: 4, H0556: 3, H0509: 3, L0602: 3, L0766: 3, L0807: 3, S0406: 3, L0624: 2, L0731: 4, L0731: 4, L0757: 4, L0601: 4, S0026: 4, H0556: 3, L0581: 3, L0608: 3, H0624: 2, L0731: 4, L0731: 2, L0744: 2, L0748: 1, H0657: 1, H0638: 1, H06
7.
1637
386
830542
376 HTTD045
376

	36-64, 76-
H0441: 1, S0280: 1, H0355: 1, H0163: 1, L0766: 1, L0809: 1, H0519: 1, H0134: 1, and	
1, H0637: 1, H0637: 1, H0637: 1, H0013: 1, S: 1, H0013: 1, S: 1, L0040: 1, S: 1, L0040: 1, S: 1, L0043: 1, H0135: 1, H0135: 1, L0768: 1, L0768: 1, L0754: 1, H0547: 1, H0543: 1, H0543: 1	H0008: 1. AR053: 6, AR055: 6 AR096: 6, AR039: 5 AR052: 4, AR060: 4 AR033: 4, AR089: 4 AR061: 3, AR104: 2 H0271: 21, H0179: 11
<u> </u>	Phe-2 to His-9, A Cys-16 to His-23, A Val-31 to Arg-37, A Pro-104 to Tyr-111. A
·	38 - 370 1792
·	830829 387
	377 HRGDD63

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						••																						-	_
79:				 -: -:		25:		43:		41:		21:		23:		30:		34:		 Ö	-			.55		82:		.9/	
6, 1.07	4,	, L07,	.; ,	, L07,	.,2	, S00	.; 2,	, H05	. <u>1</u>	, ноз	. I.	1, 1,00	₹ 1,	l, H01	5: 1,	l, H00	: 1,	l, H06): 1,	, L077	. T,	, L037	: 1,	, L066		, H06	3: 1,	l, H05	:1,
584: (F0766	748: 4	H0585	805: 3	H055(662: 2	30126	752: 2	S0040	116:1	S0360		H054	046:	H0416	290:	H0316	040:	H056	763: 1	L0761	803: 1	L0659	663: 1	30053	520: 1	H0518	134:]	L0750
8, HC	21: 5,	4, L0	55:3,	3, L0	56: 2,	2, L0	88: 2, 5	2, L0	57: 1,	1, S0	38: 1,	1, HC	31: 1,	1, HC	57: 1,	1, HC	55: 1,]	1, HC	30:1,	1, L0	59: 1,]	1, LO	6: 1,]	1, 10	.8: 1, S	1, H0	70: 1,	1, HC	54: 1,]
H0457: 8, H0584: 6, L0779:	6, H0521: 5, L0766: 4,	L0776: 4, L0748: 4, L0777:	4, H0265: 3, H0585: 3,	H0529: 3, L0805: 3, L0749:	3, H0556: 2, H0550: 2,	H0087: 2, L0662: 2, S0052:	2, L0438: 2, S0126: 2,	.0747:	2, H0167: 1, S0040: 1,	H0294: 1, S0116: 1, H0341:	, H06	10586	1, H0231: 1, H0544: 1,	H0545: 1, H0046: 1, H0123:	l, H0057: 1, H0416: 1,	H0687: 1, H0290: 1, H0030:	l, L0455: 1, H0316: 1	H0135: 1, H0040: 1, H0634:	, H0100: 1, H0560: 1	0426:	, L076	L0800: 1, L0803: 1, L0378:	1, L0806: 1, L0659: 1,	.0809:	, S042	S0216: 1, H0520: 1, H0682:	, H06	H0694: 1, H0134: 1, H0576:	1, L0754: 1, L0750: 1
<u> </u>	<u> </u>		4	<u> </u>	<u>~</u>	<u> </u>	-2		-01	<u>, 11 (</u>	, -1	<u>;4</u>		بكن		<u>;-4-i</u>	_=	. نطن		S						<u> </u>	, (<u> </u>	
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_			_													·										<u>, </u>			

	92-113, 72-88	131-147, 185-201, 113-129
L0755: 1, L0731: 1, L0758: 1, S0031: 1, S0011: 1, H0136: 1, H0423: 1 and H0422: 1.	AR052: 36, AR053: 32, AR096: 24, AR089: 16, AR033: 13, AR039: 12, AR055: 12, AR060: 10, AR104: 10, AR061: 5 S0358: 9, S0380: 2, H0656: 1, S0418: 1, H0580: 1, H0587: 1, H0632: 1, H0581: 1, H0046: 1, H054: 1, S0003: 1, T0023: 1, H0641: 1, H0529: 1, H0651: 1, S0152: 1, H0561: 1, L0747: 1, L0779: 1, L0777: 1, L0752: 1, H0445: 1 and H0422: 1.	AR096: 3, AR053: 1, AR052: 1, AR089: 1, AR060: 1, AR033: 1, AR039: 0, AR061: 0, AR104: 0, AR055: 0 L0439: 11, L0777: 10, L0803: 9, L0794: 6, L0766: 6, L0438: 6, S0358: 4, L0764: 3, L0809: 3, L0789:
L0755: 1, 1, S0031: H0136: 1, H0422: 1.		AR096: 3 AR052: AR060: 3 AR039: 0 AR104: 0 L0439: 1 L0803: 9, 6, L0438: 1 L0764::3,
	897 - 1793 Glu-10 to Arg-21, 1235 Arg-31 to Lys-47, Val-58 to Glu-63.	154 - 1794 1320
	830831 388 89	831204 389 15
	378 HTNBX62	379 HLICA76

	128-144
3, L0748: 3, L0740: 3, H0355: 2, L0435: 2, L0775: 2, L0530: 2, S0380: 2, L0747: 2, L0756: 2, L0758: 2, L0588: 2, L0362: 2, H0171: 1, H0556: 1, H0713: 1, H0583: 1, L0418: 1, S0282: 1, S0354: 1, S0376: 1, S0444: 1, S0354: 1, S0278: 1, T0040: 1, H0069: 1, H0120: 1, H0540: 1, H0046: 1, H0024: 1, H0510: 1, S6028: 1, H0615: 1, H0428: 1, L0483: 1, S0426: 1, L0796: 1, L0646: 1, L0768: 1, L0650: 1, L0375: 1, L0768: 1, L0659: 1, L0768: 1, L0659: 1, H0672: 1, H0710: 1, S0044: 1, S0406: 1, L0755: 1, L0731: 1, S0026: 1, H0710: 1, S0044: 1,	Phe-19 to Arg-27, Pro-46 to Phe-54, Ser-85 to Leu-91, Arg-115 to Thr-122.
	354 - 1795 935
	390
	831307
	HAPOA59
	380

	58-79
4, H0050: 3, L0758: 2, L0770: 2, H0039: 1, H0040: 1, L0637: 1, L0637: 1, L0637: 1, L0740: 1, L0581:	. 6, 5, 5,
AR039: 4, 10575: 3, 50126: 3, 50126: 3, 50126: 3, 10577: 3, 4, 10341: 10572: 2, 10572: 2, 10759: 1, 10139: 1, 10038: 1, 10804: 1, 10539:	10, AR033 6, AR096: 5, AR053:
AR104: 4, AR039: 4 L0766: 4, L0438: 4, H0013: 3, H0575: 3, H0050: 3, H0616: 3, S0126: 3, L0439: 3, L0757: 3, L0758: 3, H0556: 2, H0341: 2, T0110: 2, H0572: 2, L0770: 2, L0803: 2, L0759: 2, S0420: 1, S0360: 1, S0408: 1, S0132: 1, H0619: 1, S6016: 1, T0109: 1, H0318: 1, H0266: 1, S0250: 1, H0591: 1, H0135: 1, H0591: 1, H0135: 1, L0666: 1, L0664: 1, H0144: 1, H0520: 1, H0519: 1, H0696: 1, S0406: 1, H0540: 1, L0748: 1, L0740: 1, H0550: 1, L0756: 1, H0590: 1, L0756: 1, L0752: 1, L0592: 1, L0581: 1, L0752: 1, L0593: 1, L0581: 1, L0752: 1, L0593: 1, L0581:	H0423: 1. AR055: 10, AR033: AR052: 6, AR096: AR060: 5, AR053:
- C; H; H; C; H; H; H; S; S; S; G; H;	
	Arg-13 to Gln-20.
	1796 A
·	112 - 450
	391
0	831314
	HLMMX3
	381

AR061: 5, AR089: 5,		247-263, 129-145
831475 392 115 - 1797 Lys-113 to Thr-119, 990 Asp-156 to Gly-162.		2.1.
831475 392 115 - 1797 Lys-113 to Thr-119, 990 Asp-156 to Gly-162.		
831475 392 115 - 990	AR104: 5, AR089: 5, AR104: 3, AR039: 2 S0192: 7, L0803: 5, L0800: 4, L0789: 4, L0758: 4, L0804: 3, L0747: 3, H0255: 2, L0764: 2, L0659: 2, L0666: 2, L0754: 2, L0779: 2, S0420: 1, L0617: 1, S0376: 1, H0550: 1, H0618: 1, H0597: 1, H0350: 1, H0268: 1, H0622: 1, H0616: 1, H0494: 1, L0774: 1, L0656: 1, L0382: 1, L0774: 1, L0656: 1, L0382: 1, L0809: 1, H0684: 1, S0436: 1, L0601:	Lys-113 to Thr-119, Asp-156 to Gly-162.
831475		990
382 HW		HWLHW6 4

	102-120, 69-85, 50- 66
1, H0661: 1, S0356: 1, S0442: 1, S0360: 1, H0592: 1, H0590: 1, H0024: 1, H0510: 1, H0553: 1, H0024: 1, L0772: 1, L0646: 1, L0374: 1, L0673: 1, L0774: 1, L0784: 1, L0806: 1, L0653: 1, L0655: 1, S0374: 1, S0328: 1, S3012: 1, L0749: 1, L0731: 1, L0758: 1 and H0677: 1.	AR096: 5, AR033: 4, AR053: 4, AR104: 4, AR060: 3, AR052: 3, AR055: 3, AR089: 3, AR039: 2, AR061: 2 L0758: 3, S0358: 2, H0521: 2, L0439: 2, S0114: 1, H0341: 1, S0442: 1, H0734: 1, H0411: 1, H0592: 1, S0280: 1, L0021: 1, H0263: 1, S0214: 1, S0438: 1, S0422: 1, L0764: 1, L0766: 1, L0776: 1, L0783: 1, L0809: 1, L0789: 1, L0663: 1, H0696: 1, L0748: 1, L0740: 1, L0745: 1,
	Tyr-14 to Leu-27, Glu-39 to Ser-47.
	1798
	860
	393
	831577
·	HHERA41
	383

70 01/20304	1 € 17 € 5017 10
107-123, 142-158	122-150, 311-340, 1-34, 46- 65, 289- 309, 223- 243, 18-34
55: 1, L0759: 1. H0543: 1. R053: 13, R060: 12, R096: 10, R096: 10, R096: 10, R096: 10, R096: 10, R096: 1, R090: 1, H0518: R096: 1, R096: 1	17, AR096: 15, 14, AR055: 13, 11, AR060: 10, 8, AR061: 8, 7, AR039: 3 6, L0766: 4,
L0777: 1, L0755: 1, L0759: 1, L0596: 1 and H0543: 1. AR055: 14, AR053: 13, AR052: 12, AR060: 12, AR033: 10, AR096: 10, AR089: 8, AR061: 7, AR104: 6, AR039: 4 H0596: 4, L0754: 4, H0596: 2, H0616: 2, L0740: 2, L0759: 2, H0616: 2, L0740: 2, L0759: 2, H0616: 2, L0740: 2, L0759: 2, H0616: 2, L0740: 1, H0485: 1, H0156: 1, H0264: 1, S0003: 1, S0214: 1, H0581: 1, H0050: 1, H056: 1, L0651: 1, S0122: 1, H0518: 1, S0152: 1, H0522: 1, L0744: 1, L0777: 1, L0731: 1, L0758: 1, S0436: 1 and S0240: 1	AR053: 17, AR096: AR052: 14, AR055: AR089: 11, AR060: AR033: 8, AR061: AR104: 7, AR039: L0754: 6, L0766: 4,
Asn-2 to Gly-7, Thr-24 to Ser-29, Pro-65 to Ser-70, Ser-126 to Thr-132, Thr-161 to Leu-166.	O Gly-37 to Leu-43, Ala-114 to Arg-122.
1799	1800
10 - 528	304 - 1671
394	395
831638	831872
НЕХЛТ43	HE8CL14
384	385

		326-344, 172-188
S0354: 3, L0764: 3, L0803: 3, L0748: 3, H0638: 2, H0013: 2, H0051: 2, S0002: 2, L0805: 2, L0777: 2, L0731: 2, L0758: 2, L0759: 2, H0721: 2, H0624: 1, H0171: 1, H0556: 1, H0661: 1, H0486: 1, H0594: 1, S0214: 1, H0556: 1, H0594: 1, S0214: 1, H0556: 1, H0556: 1, H0594: 1, S0214: 1, H0556:	1, H0561: 1, L0761: 1, L0651: 1, L0790: 1, L0792: 1, H0648: 1, H0672: 1, L0439: 1, L0745: 1, L0779: 1, L0752: 1, L0596: 1, L0599: 1 and L0362: 1.	AR033: 5, AR089: 4, AR060: 3, AR061: 2, AR096: 1, AR053: 1, AR104: 0, AR052: 0, AR104: 0, AR039: 0 L0439: 8, L0777: 8, L0666: 4, S0010: 3, H0615: 3, L0637: 3, L0659: 3, L0664: 3, H0648: 3, L0748: 3, L0731: 3, S0412: 3, S0132: 2, S0476: 2, S0222: 2, H0497: 2, H0031: 2, L0774: 2, L0665: 2, H0144:
		Gly-22 to Arg-31, Pro-33 to Pro-40, Ala-44 to Lys-51, Ser-57 to Asp-62, Ser-68 to Lys-95.
		1801
		10-
		396
		832119
		HLWF159
		386

	43-62, 120-137, 98-114, 9- 25, 200- 216
, 10669: (10669: (100669: (100669: (100664: (100669: (100659) (100659: (100659) (100	7, 6, 6, 7, 7, 10546:
2, L0438: 2, L0754: 2, L0757: 2, L0758: 2, S0194: 2, H0171: 1, H0265: 1, H0717: 1, S0110: 1, H0669: 1, S0358: 1, S0300: 1, H0369: 1, H0550: 1, S6016: 1, S0414: 1, H0013: 1, H0628: 1, H0599: 1, H0327: 1, H0123: 1, H0553: 1, H0628: 1, L0805: 1, L0809: 1, L0663: 1, S0374: 1, S0148: 1, H0435: 1, H0659: 1, H0670: 1, S0374: 1, S0004: 1, H0696: 1, L0744: 1, L0759: 1, S0031: 1, S0434: 1, H0667: 1 and H0506: 1.	AR052: 8, AR039: 7, AR033: 7, AR061: 6, AR089: 6, AR096: 6, AR104: 5, AR055: 5, AR053: 4, AR060: 4 H0617: 5, S0418: 4, L0769: 4, L0751: 3, L0731: 3, H0657: 2, H0635: 2, H0618: 2, H0581: 2, H0546: 2, H0606: 2, H0561: 2, L0794: 2, L0439: 2, S0284:
2, L0438: 2 L0757: 2, 1 2, H0171: H0717: 1, 3 1, S0358: 1 1, S0414: 1 1, H0427: 1, 1 1, H0628: 1, 1 1, L0663: 1 20148: 1, H 1, H0670: 1, H	
	Pro-70 to Lys-75, Leu-159 to Gln-173, Arg-227 to Glu-235.
	1802 Pro
	885
	397
	832451
·	HAJCQ05
	387

	45-65, 99-	91-107, 74-90
× 4	.; 5:	7
1, H0265: 1, S0420: 1, S0358: 1, S0046: 1, H0486: 1, H0545: 1, H0318: 1, H0545: 1, H0510: 1, S0314: 1, L0483: 1, H0251: 1, H0261: 1, L0644: 1, L0764: 1, L0649: 1, L0655: 1, L0659: 1, L0666: 1, H0670: 1, H0672: 1, L0666: 1, H0670: 1, H0672: 1, S3012: 1, L0754: 1, L0758: 1, L0758: 1, H0445: 1 and H0543: 1.	AR089: 6, AR052: 6, AR060: 6, AR033: 6, AR055: 5, AR096: 4, AR053: 3, AR061: 3, AR104: 2, AR039: 1 L0748: 8, S0346: 2, H0144: 2, L0754: 2, H0656: 1, S0358: 1, S0408: 1, H0331: 1, H0620: 1, L0805: 1, L0531: 1, H0682: 1 and S0424: 1.	AR053: 3, AR033: 2, AR055: 2, AR052: 1, AR060: 1, AR061: 0, AR096: 0, AR089: 0,
	Ser-119 to Cys-125.	
	1803	1804
	208 - 597	181 -
	398	399
	832485	832587
	HAGHC54	HULAY53
	388	389

	95-113, 24-40	<u> </u>		201	85-105,	223-239			-																
																				٠					
		_									 ·		 ,								_				
	\.6. ·					-		_			.		94:		7:		177:	 -	<u>2</u>		81:		<u>'Ä</u>		72:
AR039: 0, AR104: 0	AR096: 170, AR052: 156, AR089: 119, AR060: 98, AR053: 72, AR039: 53.	AR104: 47, AR033: 42,	AR061: 39, AR055: 14					96: 0, AR052: 0,	61: 0, AR055: 0	L0439: 8, L0751: 6,	L0747: 6, L0665: 5, L0438:	4, L0779: 4, H0012: 3,	L0748: 3, H0620: 2, H0594:	2, H0424: 2, H0553: 2,	S0144: 2, L0769: 2, L0771:	2, L0809: 2, H0144: 2,	S	2, L0758: 2, L0587: 2,	H0422: 2, H0171: 1, H0664:	l, H0619: 1, S0222: 1,	H0492: 1, H0618: 1, H0581:	l, H0052: 1, H0150: 1,	H0024: 1, S0388: 1, S0364:	1, H0135: 1, H0040: 1,	.0640: 1, L0761: 1, L0372:
ARO	ARO ARO ARO	ARI	ARO	+				76, AR096:	05, AR061:				L074	2, H(S014	2, TO	H059	2, L0	H042	1, HC	H049	1, HC	H007	1, HC	L064
	Met-1 to Gly-7.			107 107	Ser-10/ to Gly-115,	Cys-202 to Thr-214,	Glu-241 to Gly-248,	Thr-265 to Leu-276,	Gly-298 to Gly-305,	Ala-382 to Gly-389,	Thr-402 to Gly-414.	•													
	1805		-	1001	1806																				
	9 - 458			600	525 -	1603																			
	400			107	401																				
	832624			270000	833067																				
	HE9DL48			111111111111111111111111111111111111111	HFKEH50																				
	390			5	391																				

W U 01/90304		FC1/US01/104
	52-69, 77- 93	65-99
1, L0773: 1, L0648: 1, L0662: 1, L0766: 1, L0774: 1, L0629: 1, L0666: 1, L0664: 1, H0658: 1, H0521: 1, S3014: 1 and H0543: 1.	AR039: 24, AR053: 17, AR052: 17, AR033: 16, AR055: 14, AR089: 13, AR096: 12, AR104: 9, AR060: 9, AR061: 7 L0758: 4, H0014: 1, S0051: 1, H0038: 1, H0413: 1, H0529: 1, L0770: 1, L0769: 1, L0794: 1 and L0752: 1.	AR055: 11, AR061: 7, AR096: 7, AR089: 6, AR030: 6, AR052: 6, AR039: 1, AR104: 0 L0761: 7, L0747: 6, S0045: 4, L0766: 4, L0755: 4, L0770: 3, S0126: 3, L0731: 3, H0657: 2, H0730: 2, L0623: 2, H0546: 2, H0150: 2, H0012: 2, H0620: 2, H0529: 2, H0739: 1, S6024: 1, T0049: 1, H0381: 1, H0663: 1, H0306: 1,
	3, 121, 58.	Arg-8 to Glu-15, Gln-38 to Gln-43, Thr-50 to Arg-68, Gln-95 to Gln-106.
	1807	1808
	- 966 - 475	73 - 420
	402	403
	834541	834610
	HUSXK49	HTSFU12
	392	393

	54-78
	•
H0549: 1, S0222: 1, H0586: 1, H0599: 1, T0048: 1, H0599: 1, T0048: 1, H0597: 1, H0544: 1, H0545: 1, H0567: 1, H0571: 1, H0642: 1, H0677: 1, H0642: 1, H0617: 1, L0055: 1, L0142: 1, H0617: 1, L0055: 1, L0763: 1, L5655: 1, L0763: 1, L0809: 1, L0806: 1, L0805: 1, L0776: 1, L0763: 1, L0383: 1, S0296: 1, S0380: 1, H0710: 1, H0631: 1, L0611: 1, S0027: 1, L0757: 1, L0588: 1, H0423: 1 and H0506: 1.	AR055: 15, AR039: 10, AR096: 9, AR089: 8, AR033: 8, AR053: 8, AR052: 7, AR060: 7, AR061: 6, AR104: 6 L0439: 5, L0747: 5, L0731: 4, L0499: 2, L0774: 2, L0805: 2, L0665: 2, L0438: 2, L0743: 2, L0744: 2, L0757: 2, L0759: 2, H0556: 1, H0713: 1, H0583:
	Pro-12 to Thr-38, Tyr-86 to Trp-92, Glu-142 to Trp-150.
	3 - 1809
	404 978 - 394
d	834810
	394 HELHM15
	394

	65-102, 85-102	136-162
1, S0045: 1, H0587: 1, H0486: 1, H0599: 1, H0581: 1, H0530: 1, H0544: 1, H0163: 1, H0090: 1, H0100: 1, L0770: 1, L5566: 1, L0364: 1, L0649: 1, L0803: 1, L0659: 1, L0809: 1, L0789: 1, L0352: 1, S0380: 1, L0749: 1, L0750: 1, L0758: 1, L0581: 1 and H0667: 1.	10 Pro-17 to Pro-23, AR053: 23, AR052: 20, Arg-40 to Tyr-50, AR096: 18, AR055: 16, Arg-143 to Ala-154. AR060: 13, AR089: 13, AR104: 9, AR061: 9, AR033: 9, AR039: 7 H0616: 3, L0758: 3, L0717: 1, H0038: 1 and L0779: 1.	1 Asp-9 to Asn-21, AR096: 5, AR052: 3, Bro-24 to Ser-38, AR089: 3, AR033: 2, Thr-54 to Tyr-61, AR053: 2, AR060: 2, Asp-126 to Asn-131, AR039: 2, AR055: 1, Asp-133 to Asp-138, AR061: 1, AR104: 0 Cys-167 to Ile-175. H0641: 10, H0521: 10, H0575: 6, L0599: 6, H0638: 4, H0435: 3, L0758: 3, L0600: 3, H0616: 2, H0413: 2, H0423: 2, T0049: 1,
	665 - 1810	174 - 181 698
	931 405	271 406
	395 HTEJP13 834931	396 НDQНВ46 835271

	101-134, 22-38, 124-140, 49-65		180-214	154-190,
H0657: 1, H0580: 1, H0486: 1, H0042: 1, H0123: 1, H0375: 1, H0031: 1, H0038: 1, H0412: 1, H0652: 1, L0787: 1, H0518: 1, H0522: 1 and H0707: 1.	AR033: 8, AR055: 2, AR039: 2, AR061: 2, AR089: 2, AR060: 1, AR096: 1, AR104: 1, AR052: 0, AR053: 0 L0439: 25, L0438: 5, L0742: 5, S0010: 4, S0412: 2, S0222: 1, H0592: 1, H0013: 1, H0156: 1, H0194: 1, H0178: 1, H0024: 1, S0051: 1, T0010: 1, L0455:	1, S0036: 1, L0371: 1, L0794: 1, L0809: 1, H0547: 1, H0539: 1 and L0786: 1.	AR053: 67, AR052: 49, AR096: 48, AR089: 35, AR039: 25, AR060: 22, AR104: 20, AR033: 16, AR055: 8, AR061: 6 H0486: 2	AR055: 5, AR053: 4, AR060: 3, AR061: 3,
·				Trp-6 to Ala-14, Ala-33 to Gly-43,
	1812		1813	1814
	158 - 595		123 - 896	813 -
1	407		408	409
	835488		835717	835896
	нсете50		HDTB048	399 HODGL01
	397		398	399

												,	_																
				45:		:56:		.62:		55:		74:		16:		22:		74:	-	12:		551:		03:	_	93:		<u>748:</u>	
AR033: 3, AR052: 3,	AR089: 3, AR039: 3,	AR096: 2, AR104: 1	H0250: 9, H0271: 7,	.0743: 6, L0751: 6, L0745:	6, S0360: 5, H0265: 4,	.0666: 4, H0521: 4, H0556:	, H0716: 3, S0280: 3,	.0662: 3, H0713: 2, H0662:	S0278: 2, H0486: 2,	H0615: 2, L0805: 2, L0655:	2, L0664: 2, H0672: 2,	S0378: 2, L0746: 2, S0434:	L0581: 2, S0196: 2,	H0650: 1, H0656: 1, S0116:	l, S0420: 1, S0444: 1,	580: 1, H0619: 1, S60	1, H0635: 1, H0427: 1,	.0021: 1, H0253: 1, S0474:	1, H0457: 1, H0355: 1,	S0334: 1, H0286: 1, S0312:	1, H0252: 1, H0032: 1,	H0634: 1, H0063: 1, H0551:	S0440: 1, H0649: 1,	L0771: 1, L0649: 1, L0803:	L0774: 1, L0806: 1,	.0636: 1, L0791: 1, L0793:	1, L0665: 1, H0690: 1,	H0670: 1, H0660: 1, H0648:	1, H0518: 1, S0174: 1,
Trp-68 to His-73. Al		A	<u> </u>	21	<u>,</u>	<u>3</u>	3,	27	Ċ.	H	ZÍ.	<u>S</u>	<u>2</u>)H	1,)H	1,	21	1,	<u>S</u>	-	H		3	<u> </u>	21	H	Ħ.	1,
																													
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	117-133, 90-106	143-176
H0555: 1, H0436: 1, S0032: 1, L0744: 1, H0343: 1, L0584: 1, S0242: 1, H0422: 1 and H0506: 1.	AR061: 3, AR096: 2, AR055: 2, AR060: 2, AR104: 2, AR033: 1, AR052: 1, AR039: 1, AR052: 1, AR039: 0 H0046: 2, H0009: 2, H0090: 2, H0494: 2, L0438: 2, H0547: 2, H0521: 2, L0439: 2, L0777: 2, H0543: 2, H0556: 1, S0342: 1, S0045: 1, H0619: 1, H0632: 1, S0003: 1, L0483: 1, H0628: 1, H0623: 1, H0561: 1, L0761: 1, L0803: 1, L0804: 1, L0659: 1, L0382: 1, H0144: 1, H0539: 1, S0152: 1, H0478: 1, H0631: 1, L0741: 1, L0740: 1 and L0591: 1.	AR096: 1, AR039: 1, AR052: 1, AR104: 1, AR061: 1, AR089: 1, AR055: 1, AR053: 0,
	15 Pro-45 to Gln-55.	
	1815	1816
	2150	17 - 619
	410	411
	835965	836191
	HE8TO35	нонсвое
	400	401

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																			•									•	
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AR060: 0, AR033: 0	L0744: 8, L0777: 8,	L0749: 6, S0126: 4, S0358:	3, H0622: 3, L0805: 3,	H0519: 3, H0624: 2, S0476:	2, L0717: 2, H0486: 2,	H0012: 2, S0250: 2, L0662:	2, L0803: 2, L0659: 2,	L0519; 2, L0663; 2, L0438;	2, H0520: 2, H0435: 2,	L0751: 2, L0747: 2, L0759:	2, H0685: 1, S0212: 1,	S0442: 1, H0729: 1, H0550:	1, H0013: 1, S0280: 1,	H0599: 1, H0575: 1, H0123:	1, L0471: 1, H0057: 1,	H0266: 1, H0687: 1, H0292:	1, H0688: 1, H0030: 1,	H0644: 1, T0041: 1, L0770:	1, L0771: 1, L0768: 1,	L0774: 1, L0655: 1, L0661:	1, L0665: 1, H0724: 1,	H0547: 1, S0330: 1, H0539:	1, H0518: 1, S0152: 1,	H0555: 1, S0390: 1, L0748:	1, L0439: 1, L0740: 1,	L0779: 1, L0755: 1, L0731:	1, H0595: 1, L0591: 1,	L0593: 1, S0192: 1 and	S0196: 1.
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			-																			<u> </u>			_	·			

116-138, 202-226, 49-67, 148-166, 270-286, 174-190, 99-115, 22-38, 1-	301-328, 288-304
Arg-195 to Phe-203, AR033: 380, AR061: 335, Ser-258 to Thr-264. AR060: 243, AR104: 243, AR055: 238, AR096: 231, AR089: 178, AR053: 132, AR052: 131, AR039: 122 L0750: 2, H0580: 1, S0010: 1, T0110: 1, H0457: 1, H0436: 1, L0779: 1, L0752: 1 and H0543: 1.	AR033: 2, AR053: 2, AR089: 2, AR060: 2, AR052: 1, AR096: 1, AR039: 1, AR051: 1, AR055: 0 L0750: 8, H0318: 6, L0747: 5, L0438: 5, L0747: 5, S0442: 4, H0046: 4, L0655: 4, L0809: 4, L0666: 4, L0740: 4, S0356: 3, S0444: 3, H0486: 3, L0766: 2, L0776: 2, L0773: 2, L0776: 2, L0659: 2, L0777: 2, S0436: 2, L0777: 2, S0436: 2, L0777: 2, S0436: 2, L0596: 2, L0591: 2, L0362: 2, H0542: 2, H0551: 2, L0777: 2, S0436: 2, L0591: 2, L0362: 2, H0542: 2, H0506: 2, L0591: 2, L0362: 2, H0542: 2, H0575:
Arg-195 to Phe-203, Ser-258 to Thr-264.	Tyr-20 to Asn-26, Ala-37 to Ser-46, Thr-99 to Glu-105, Cys-163 to Arg-171, Tyr-204 to Leu-215, His-279 to Phe-285, Ala-334 to Ala-349, Ala-363 to Gly-379.
1817	1818
173 -	130 - 1266
412	413
836762	836997
402 H2CBN10 836762	HBJNB08
402	403

	41-57, 77- 98	
		<u> </u>
1, H0590: 1, S0010: 1, S0346: 1, H0705: 1, H0581: 1, H0052: 1, T0110: 1, H0597: 1, H0239: 1, H0622: 1, H0644: 1, H0674: 1, H0163: 1, H0591: 1, H0038: 1, H0087: 1, H0100: 1, S0448: 1, S0440: 1, S0142: 1, H0529: 1, L0763: 1, L0804: 1, L0775: 1, L0651: 1, L0806: 1, L0805: 1, L0783: 1, L0790: 1, L0791: 1, L0664: 1, H0701: 1, H0593: 1, H0670: 1, H0539:	1, S0406: 1, S3012: 1, S0028: 1, L0439: 1, L0751: 1, L0755: 1, H0445: 1, S0434: 1, H0423: 1 and S0424: 1. AR096: 1, AR089: 1, AR104: 1, AR033: 1, AR061: 1, AR060: 0, AR055: 0, AR052: 0,	H0599: 2, L0663: 2, S0136: 2, L0740: 2, S0418: 1, H0550: 1, H0592: 1, H0587: 1, H0373: 1, H0090: 1, S0422: 1, L0763: 1, S0052: 1, S0013: 1, H0696:
	1, Ser-3 to Gly-12, Ala-16 to Arg-28, Lys-62 to Leu-68. A	
	1819	
	110 -	
	414	
	837474	
	HHAMF80	
•		

124-143	58-74	26-42, 55- 71, 145- 161, 110- 126
1 and 7, 4, 3, 3,	11, 1, 0, 0, 0, 0, 1 and 1 and	2, 1, 1, 0, 7, L0404: 1,
1, L0749: 1, L0779: 1 and L0485: 1. AR060: 12, AR096: 7, AR039: 5, AR053: 4, AR052: 3, AR033: 3, AR055: 3, AR089: 3, AR104: 3, AR061: 2 S6022: 1, H0486: 1,	H0560: 1, L0565: 1 and H0521: 1. AR089: 1, AR104: 1, AR061: 0, AR039: 0, AR055: 0, AR096: 0, AR060: 0, AR052: 0 S0386: 2, S0420: 1, H0013: 1, H0457: 1, S0250: 1, S0390: 1, L0596: 1 and	H0422: 1. AR104: 6, AR061: 2, AR096: 2, AR060: 1, AR053: 1, AR089: 1, AR052: 0 L0745: 12, L0771: 7, L0766: 3, L0746: 3, L0777: 3, L0764: 2, L0775: 2, L0779: 2, L0757: 2, L0404: 1, S0360: 1, H0351: 1,
1, L0749: L0485: 1. AR060: AR039: AR052: AR104: S6022: 3	H0560: 1 H0521: 1 AR089: AR053: AR061: AR060: S0386: 2 H0013: 1 1, S0390:	
1820 Gly-10 to Phe-18, Gly-28 to Asp-40.	Gln-10 to Arg-16, Leu-31 to Thr-38, Val-49 to Arg-55, Cys-77 to Ser-82, Ser-102 to Ala-107.	Leu-14 to Asp-19, Gly-47 to Trp-55, Ser-102 to Ser-107, Asp-136 to Cys-143.
1820 G	1821 G L L V V C C C	1822 L G S S A
199 - 771	183 - 656	22 - 531
415	416	417
837522	837523	837526
HDPUR66	HBWBX66	407 HMHBR95
405	406	407

VO 01/90304	
	82-99
,	
H0441: 1, H0069: 1, H0052: 1, H0288: 1, H0286: 1, S0364: 1, H0634: 1, H0264: 1, H0494: 1, H0646: 1, L0772: 1, L0372: 1, L0800: 1, L0778: 1 and H0672: 1.	AR089: 11, AR060: 8, AR096: 8, AR096: 8, AR033: 6, AR052: 4, AR053: 4, AR059: 4, AR104: 4, AR055: 3, AR061: 3 L0744: 9, L0731: 8, L0748: 4, L0748: 4, L0745: 4, L0758: 4, S0040: 3, H0013: 3, H0038: 3, S0344: 3, L0769: 3, L0773: 3, L0755: 2, S0356: 2, S0358: 2, H0550: 2, H0620: 2, L0775: 2, H0598: 2, S0036: 2, L0775: 2, L0776: 2, L0775: 2, L0776: 2, L0775: 2, L0776: 2, L0775: 2, L0776: 2, L0775: 2, H0539: 2, S0126: 2, H0539: 2, S0126: 2, H0539: 2, S0126: 2, H0521: 2, S3014: 2, L0754: 2, L0747: 2,
E-S-L-E	Gly-24 to Gly-29, A Ala-47 to Pro-52. A Ala-47 to Pro-52. A S S S S S S S S S S S S S S S S S S
	1823
	5 - 388
	418
÷	837527
	HEGAU68
	408

L0780: 2, L0752: 2, L0757: 2, L0503: 2, H0170: 1, 1, L0603: 2, H0170: 1, 1, L0603: 2, H0170: 1, 1, S0114: 1, L0427: 1, 1, S0114: 1, L0427: 1, 1, S0114: 1, L0427: 1, 1, S0104: 1, S0354: 1, 1, S0420: 1, S0354: 1, 1, S0435: 1, S0354: 1, 1, S0435: 1, S0356: 1, H0208: 1, 1, S0435: 1, S0356: 1, H0208: 1, 1, S04376: 1, S0278: 1, H0549: 1, 1, H0433: 1, H0497: 1, H0438: 1, H0497: 1, H0405: 1, H0608: 1,							
	0780: 2, L0752: 2, L0757: , L0591: 2, L0608: 2, 0362: 2, L0361: 2, L0601: , L0603: 2, H0170: 1,	.0265: 1, H0556: 1, 10002: , S0114: 1, L0427: 1, 0116: 1, S0282: 1, H0402: , S0420: 1, S0354: 1, 0376: 1, S0360: 1, H0208:	, \$0045: 1, \$0132: 1, 0476: 1, \$0278: 1, H0549: , \$0222: 1, \$6014: 1, 0441: 1, H0438: 1, H0497:	, H0333: 1, H0069: 1, 0021: 1, H0618: 1, S0010: , H0421: 1, H0251: 1, 0085: 1 H0327: 1 H0150:	, H0178: 1, H0050: 1, [0024: 1, H0051: 1, H0375: , H0594: 1, H0188: 1, [0687: 1, S0022: 1, H0252:	, H0615: 1, H0428: 1, 10622: 1, H0031: 1, H0644: , H0673: 1, H0674: 1, 10135: 1, H0163: 1, H0634: H0087: 1, H0412: 1	10056: 1, \$0038: 1, H0100: , T0041: 1, H0429: 1, 0450: 1, \$0142: 1, \$0426: , H0529: 1, L0763: 1,
		1, 1, E	E SC 1,	1, E	用·抗压力		HH 11, S(
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	234-252, 18-34
L0770: 1, L0796: 1, L0761: 1, L0667: 1, L0646: 1, L0764: 1, L0771: 1, L0766: 1, L0375: 1, L0659: 1, L0657: 1, L0659: 1, L0543: 1, L0689: 1, L0543: 1, L0666: 1, L0664: 1, H0703: 1, S0374: 1, H0520: 1, H0619: 1, H0689: 1, H0682: 1, R0659: 1, H0658: 1, S0328: 1, S0404: 1, S0406: 1, S0027: 1,	1, 1072. 1, 11077. 1, 1107
	419 10
	1 837597
	409 HMEAD61

	74-97, 29-
L0769: 2, L0662: 2, L0665: 2, L0747: 2, L0777: 2, H0445: 2, H0543: 2, H0170: 1, H0394: 1, H0556: 1, T0002: 1, H0662: 1, S0046: 1, L0717: 1, H0392: 1, H0497: 1, H0253: 1, H0318: 1, H0544: 1, H0178: 1, L0157: 1, L0471: 1, H0291: 1, T0010: 1, H0408: 1, H0266: 1, H0188: 1, H0290: 1, S0022: 1, H0135: 1, H0690: 1, H0040: 1, H0634: 1, L0700: 1, L0637: 1, L0771: 1, L0521: 1, L0768: 1, L0771: 1, L0659: 1, L0771: 1, L0663: 1, L0664: 1, L0629: 1, L0663: 1, L0664: 1, H0519: 1, H0682: 1, H0539: 1, H0521: 1, H0522: 1, H0519: 1, H0667: 1, H0542: 1, H0134: 1, H0214: 1, L0779: 1, H0667: 1, H0542: 1	AR096: 5, AR061: 4, AR039: 3, AR033: 3, AR053: 3, AR060: 3, AR055: 3, AR052: 3,
2,1 1,1 1,0 1,1 1,1 1,1 1,1 1,1 1	Pro-20 to Ser-28, Gly-59 to Leu-69, Tyr-101 to Ile-106.
	61 - 477 1825
	837726 420
	410 HDTDF94

	52
	62
AR089: 2, AR104: 2 L0748: 5, H0024: 2, L0439: 2, H0662: 1, S0420: 1, S0132: 1, H0431: 1, H0586: 1, H0486: 1, H0013: 1, H0575: 1, L0518: 1, H0539: 1, H0521: 1, S0242: 1 and S0194: 1.	AR096: 2, AR055: 1, AR089: 1, AR033: 1, AR060: 1, AR052: 1, AR061: 1, AR039: 0, AR061: 1, AR039: 0, AR053: 0 L0754: 118, L0748: 42, H0553: 29, L0777: 15, L0755: 13, L0603: 11, H0030: 10, H0031: 10, H0064: 6, L0740: 6, L0142: 5, H0100: 5, L0731: 4, L0065: 3, H0551: 2, H0494: 2, L0439: 2, L0747: 2, L0749: 2, L0780: 2, S0242: 2, H0657: 1, S0418: 1, H0053: 1, H0051: 1, H0328: 1, H0615: 1, L0143: 1, L0471: 1, H0413: 1, L0666: 1, L0663: 1, H0518: 1, S0332: 1, S0454: 1, H0704: 1, H0555: 1, L0756:
AR LO LO LO HO 1, J	i o
	Glu-2 to Ala-19, Leu-23 to Gln-40.
	1826
	421
	837785
	HKAJL51
	411

	,,,,,,,	•																								
	163-193, 21-56 9-	26, 59-77,	183-199				161-190,	232-254,	111-138,	200-216,	66-82,	137-153,	26-42												75-92	
																- 10.			-	-						
1, L0601: 1, S0011: 1 and H0136: 1.	AR096: 3, AR061: 2,		_		H0615: 2, H0040: 1,	H0272: 1 and H0436: 1.	AR039: 4, AR096: 3,	AR052: 3, AR053: 3,	AR089: 3, AR033: 2,	AR055: 2, AR061: 2,		H0586: 6, L0777: 5,	H0661: 3, S0476: 2, H0592:	2, H0587: 2, H0494: 2,	S0001: 1, H0486: 1, H0013:	1, S0280: 1, H0251: 1,	.0738: 1, S0214: 1, H0488:	1, L0369: 1, L0770: 1,	_0637: 1, L0772: 1, L0659:	1, L0647: 1, L0666: 1,	H0724: 1, H0519: 1, H0682:	1, S0027: 1, S0028: 1,	S0206: 1, L0747: 1, L0755:	l and H0595: 1.	AR033: 1, AR096: 1,	AR104: 1, AR089: 0,
11,		Sel-39 to Sel-100, Al Pro-134 to His-140. Al		IA	-	H	Met-1 to Gly-7, AJ	Cys-47 to Arg-52, AI		1.	_		H	ZÍ.	<u>S</u>	1	3	<u>T</u>	ĭ		H	<u></u>	OS		1829 Ser-4 to Asn-10, Al	Pro-29 to Cys-38, Al
	1827						1828																		1829	
	419-	1024					172 -	1044																	544 -	1812
	422						423		-																424	
	837858						838145																		838619	
	HODGZ47						HTJM074	,	•																нонсе56	
	412						413		_																414	

2055: 0,	0, AR060: 0,		620: 8,	31: 8, L0742:	0486: 5,	50: 4, L0747:	0039: 3,	54: 3, L0780:	0294: 2,	86: 2, H0253:	0545: 2,	24: 2, H0622:	0036: 2,	12: 2, H0494:	3806: 2,	89: 2, H0435:	0740: 2,	79: 2, L0777:	0755: 2,	92: 2, H0624:	0295: 1,	20: 1, L0619:	0208: 1,	00: 1, H0351:	[0455: 1,	75: 1, H0544:	(0081: 1,	51: 1, H0594:	0551: 1,
Chr-70, AR061: 0, AR055:	AR039:	, <u>۸</u>			_	Leu-258, H0012: 4, S0250: 4, L0747:		Phe-350, L0770: 3, L0654: 3, L0780:	``	Arg-423. L0149: 2, H0586: 2, H0253:		H0050: 2, H0024: 2, H0622:	2, H0124: 2, S0036: 2,	H0135: 2, S0112: 2, H0494:	2, L0662: 2, L0806: 2,	L0659: 2, H0689: 2, H0435:	2, L0741: 2, L0740: 2,	L0751: 2, L0779: 2, L0777:	2, L0752: 2, L0755: 2,	L0366: 2, S0192: 2, H0624:	1, S6024: 1, H(H0484: 1, S0420: 1, L0619:	1, S0356: 1, H0208: 1,	S0046: 1, S0300: 1, H0351:	1, H0549: 1, H0455: 1,	H0333: 1, H0575: 1, H0544:	1, H0123: 1, H0081: 1	S0050: 1, S0051: 1, H0594:	1, S0022: 1, H0551: 1,
Pro-64 to Thr-70,	Glu-95 to Tyr-100,	Lys-106 to Arg-115,	Thr-139 to Ser-146,	Arg-160 to Glu-166,	Gly-205 to Gly-218,	Ser-252 to Leu-258,	Gly-278 to Thr-288,	Gln-340 to Phe-350,	Ser-378 to Gly-391,	Gly-398 to Arg-423.	•																		
																											-		
																	·												

:
1, MO328: 1, H0688: 1, H0428: 1, H0039: 1, H0169: 1,

	1-24, 61- 88, 53-70, 35-51	140-158, 22-38, 237-254, 105-121, 210-226
<u></u>		<u> </u>
H0135: 1, H0372: 1, H0494: 1, H0560: 1, H0633: 1, S0144: 1, H0529: 1, L0654: 1, H0520: 1, H0435: 1, H0660: 1, S0330: 1, L0602: 1, L0439: 1, L0731: 1, H0668: 1, H0665: 1 and H0542: 1.	AR096: 8, AR089: 6, AR060: 5, AR052: 5, AR053: 5, AR033: 4, AR055: 4, AR039: 3, AR061: 3, AR104: 2 S0053: 2, H0171: 1 and S0037: 1.	AR053: 1, AR104: 1, AR033: 1, AR060: 1, AR089: 0, AR096: 0, AR039: 0, AR052: 0, AR039: 0, AR055: 0 L0766: 7, L0758: 3, L0759: 3, H0038: 2, H0560: 2, L0804: 2, L0775: 2, L0751: 2, L0779: 2, L0595: 2, H0656: 1, S0212: 1, H0664: 1, S0354: 1, L0011: 1, H0156: 1, H0599: 1, S0346: 1, H0581: 1, H0673: 1, H0591: 1, H0413: 1,
	Arg-31 to Asn-36.	1832 Met-1 to Gly-7, Ala-45 to Gly-53, Leu-76 to Phe-84, Lys-135 to Thr-141.
	1831	1832
	661 - 1014	349 - 1170
	426	427
	838860	839006
	HSHCL04	HAJBR52
	416	417

	1-25, 35- 56, 188- 210, 85- 107, 155- 171, 61-77	
L0370: 1, L0642: 1, S0428: 1, H0555: 1,	1, 1, 1, 1, 1, 5, 2, 2, 5, 2, 30031: 2, 1, 1, 1, 1,	T'0010: , H'0606: ,
H0623: 1, S0038: 1, L0370: 1, H0561: 1, S0422: 1, L0770: 1, L0772: 1, L0642: 1, L0656: 1, L0663: 1, S0428: 1, H0519: 1, S0330: 1, H0579: 1, H0576: 1, L0588: 1, L0605: 1 and H0667: 1.	AR033: 2, AR104: 1, AR055: 1, AR060: 1, AR052: 1, AR096: 1, AR089: 1, AR061: 1, AR053: 1, AR039: 0 S0278: 13, S0144: 12, S0142: 9, H0521: 8, S0222: 6, S0282: 5, H0638: 5, S0344: 5, S0028: 5, L0731: 5, S0001: 4, S0045: 3, S0049: 3, L0755: 3, S0031: 3, H0351: 2, S0428: 2, L0756: 2, H0624: 1, H0716: 1, H0455: 1, H0333: 1, H0575: 1, H0052: 1, H0041: 1,	H0009: 1, N0006: 1, T0010: 1, H0375: 1, S6028: 1, H0416: 1, H0617: 1, H0606: 1, H0068: 1, S0036: 1, S0112: 1, S0438: 1, S0440:
H0623: 1, 1, H0561: 1, H0561: 1, L0770: 1, 1, L0656: 1, 1, H0519: H0539: 1, H0576: L0605: 1		H0009: 1, 1, H0375: H0416: 1, 1, H0068: S0112: 1,
	Thr-184 to Phe-190, Thr-219 to Ser-226.	
	1833	
	53 - 730	
	428	
	839237	
	HSLEK65	
	418	

	41-68	
: 1, , L0806: : 1, , S0332: : 1, and	2: 29, 3: 26, 3: 26, 5: 18, 1: 12 1: 12, 1: 10769: 1: 5, 1: 10750: 1: 4, 1: 10775: 1: 3, 1: 10351:	: 2, ; H0670: : 2, ; S0436: : 1, ; H0484:
1, S0002: 1, L0763: 1, L0769: 1, L0637: 1, L0806: 1, L0658: 1, L0666: 1, S0126: 1, L0355: 1, S0332: 1, H0522: 1, S0044: 1, S0390: 1, S0436: 1 and L0599: 1.	AR033: 29, AR052: 29, AR039: 28, AR053: 26, AR104: 25, AR089: 23, AR096: 19, AR055: 18, AR060: 14, AR061: 12 L0805: 51, L0776: 33, L0741: 8, L0438: 7, L0769: 6, L0777: 6, H0052: 5, H0617: 5, L0748: 4, L0750: 4, L0779: 4, L0753: 4, H0424: 3, S0036: 3, L0775: 3, L0809: 3, S0378: 3, S0040: 2, L0103: 2, H0024: 2, T0006: 2, H0284: 2, T0006: 2, H0213: 2, S0038: 2, L0351:	2, L0764: 2, L0768: 2, L0794: 2, L0659: 2, H0670: 2, L0602: 2, L0747: 2, L0731: 2, L0758: 2, S0436: 2, L0592: 2, S0342: 1, S0282: 1, S0030: 1, H0484: 1, S0007: 1, S0278: 1,
1, S0002 L0769: 1 1, L0658 S0126: 1 1, H0522 S0390: 1 L0599: 1	7.	2, L07 L0794 2, L06 L0731 2, L05 S0282 1, S00
	Met-1 to Thr-7, Leu-24 to Glu-31, Gln-34 to Gly-44, Gly-82 to Ser-87, Asp-94 to Leu-99, Ala-102 to Glu-107.	
	1834	
	315 - 650	
	429	
	839272	
	HWGAF42	
	419	

	177-193
·	
H0261: 1, S0222: 1, H0441: 1, H0156: 1, T0082: 1, H0194: 1, H0231: 1, T0010: 1, S6028: 1, H0271: 1, L0483: 1, H0418: 1, H0412: 1, S0370: 1, S0144: 1, S0002: 1, L0520: 1, L0762: 1, L0653: 1, L0638: 1, L0791: 1, L0665: 1, L0788: 1, L0791: 1, L0665: 1, L0367: 1, H0539: 1, S0032: 1, L0742: 1, L0740: 1 and H0667: 1.	AR033: 5, AR055: 5, AR089: 4, AR052: 4, AR060: 4, AR096: 4, AR053: 4, AR061: 4, AR104: 2, AR039: 0 H0553: 3, H0494: 3, L0748: 3, H0457: 2, H0031: 2, H0521: 2, S0040: 1, S0218: 1, H0662: 1, S0418: 1, S0354: 1, S0045: 1, H0411: 1, H0549: 1, H0586: 1, H0497: 1, H0331: 1, H0486: 1, H0013: 1, H0036: 1, H0050: 1, S0036: 1, L0370: 1, S0002: 1, L0766:
	Ser-10 to Asp-28, Ser-51 to Arg-85, Val-92 to Asn-97, Tyr-123 to Gly-133, Glu-138 to Lys-145, Thr-265 to Gly-276, Thr-303 to Gln-308, Leu-314 to Thr-321, Leu-314 to Thr-339, Lys-347 to Leu-354.
	1835
	375 - 1598
	430
	839547
	HOUEA63
	420

101/000/1010
241-268
166800, 210900
15q26.1
1836 Ala-4 to Asn-18, AR096: 3, AR033: 2, Leu-69 to Gln-75, AR061: 2, AR089: 2, Asp-114 to Pro-119, AR053: 2, AR052: 2, Ala-153 to Arg-162, AR039: 1, AR104: 1 Ala-209 to Ser-244. L0748: 15, L0439: 10, H0046: 9, L0758: 8, L0596: 7, L0589: 7, H0013: 6, L0769: 6, L0666: 6, H0556: 5, H0341: 5, S0420: 5, H0579: 4, H0579: 4, H0579: 4, H0032: 4, H0579: 3, H0656: 3, S0476: 3, H0657: 3, H0657: 3, H0657: 3, H0657: 3, H0687: 3, H0687: 3, H0687: 3, H0687: 3, H0687: 3, H0687: 3, H0579: 3, H0579: 3, H0579: 3, L0779: 4, L0779
213 - 1133
431
839561
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3, F	4:2	2, S	3	2, T	7:2	2, F	6:2	2, F	4:2	2, I	1:2	王;	÷.2	2, T	1:2	7, T	9:2	2,5	 2,	2, T	1:2	2, H	5:2	2, I	3: 1	1, 5	0:1	H,	1:1
2	113	33:	8	3	25	18:	359	12:	312	4.	256	0.2	52	4	7,77	5:	965	10:	027	<u></u>	73	5:	50	52:	071	95:	965	Ξ	990
0,0	S.	<u>§</u>	S,	022	Ħ,	103	H,	9	Ħ,	Ĭ02	Ħ,	<u>₹</u>	H(970	Ä	965	H,	107	SS.	975	٦,	8	H,	103	H,	102	H,	8	H,
3, I	4.2	2, H	2.	2, S	9.2	2, F	2.	2, F	9.2	2, F	3:2	Š	2.7	2, L	2:2	2, T	3:2	2, F	4:2	2, L	2	ر ا	4.2	2, F	6: 1	1, F	3: 1	l, S	5: 1
15:	962	6:5	<u>5</u>	9	90	<u>&</u>	05	90)16	33:	962	2.7	42	ë.∷	399	5: ,	438		017	4)3/2	<u>;;</u>	42		99	7:)58	ö	25
H0445: 3, L0592: 3, H0677:	3, H0624: 2, S0134: 2,	S0116: 2, H0483: 2, S0360:	2, S0045: 2, S0046: 2,	H0619: 2, S0222: 2, T0039:	Ħ,	H0599: 2, H0318: 2, H0581:	2, H0052: 2, H0596: 2,	H0150: 2, H0012: 2, H0014:	2, H0169: 2, H0124: 2,	H0163: 2, H0264: 2, H0412:	2, H0623: 2, H0561: 2,	S0382: 2, S0440: 2, H0652:	2, S0426: 2, H0529: 2,	.0640: 2, L0764: 2, L0773:	2, L0662: 2, L0774: 2,	.0375: 2, L0655: 2, L0526:	2, L0438: 2, H0659: 2,	H0658: 2, H0710: 2, S0404:	2, S3014: 2, S0027: 2,	.0754: 2, L0750: 2, L07	Z,	.0588: 2, L0485: 2, H0422:	2, S0424: 2, H0506: 2,	H0008: 2, H0352: 2, H0220:	1, H0686: 1, H0713: 1,	H0717: 1, H0295: 1, S0430:	1, H0583: 1, H0650: 1	S0110: 1, S0001: 1, H0484:	1, H0255: 1, H0661: 1
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H0663: 1, H0664: 1, H0662:	S0376: 1, S0444: 1, S0408:	1, S0132: 1, H0393	L0717: 1, H0351:	1, H0261: 1, H0403: 1,	H0592: 1, H0586: 1, H0497:	1, H0333: 1, H063	H0257: 1, H0486: 1, H0250:	1, H0075: 1, H0635: 1,	H0036: 1, H0590: 1, H0253:	1, H0421: 1, T0103: 1	T0110: 1, H0327: 1, H0545:	1, H0009: 1, H012	H0050: 1, H0051: 1, S0051:	1, T0010: 1, H0355: 1	H0188: 1, H0288: 1, S0312:	1, S0314: 1, H0615: 1,	H0039: 1, H0622: 1, L0455:	1, S0366: 1, H0598	H0135: 1, H0040: 1, H0413:	1, H0056: 1, H0100: 1	L0435: 1, L0564: 1, H0494:	1, L0475: 1, H0334: 1,	H0560: 1, H0641:	1, H0647: 1, H064	S0344: 1, S0208: 1, S0210:	1, L0369: 1, L0763:	L0770: 1, L0667: 1, L0772:	1, L0372: 1, L0800:
																												
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	74-91	88-106, 246-262, 63-79, 169-185
		134570, 601090, 602028
		6p25-p24
L0521: 1, L0803: 1, L0650: 1, L0651: 1, L0653: 1, L0783: 1, L0383: 1, L0647: 1, S0428: 1, S0216: 1, S0374: 1, H0724: 1, L0352: 1, H0690: 1, H0435: 1, H0555: 1, H0627: 1, S3012: 1, S0037: 1, S0032: 1, L0749: 1, L0749: 1, L0756: 1, L0779: 1, L0749: 1, L0756: 1, L0779: 1, L0759: 1, L0759: 1, L0759: 1, L0593: 1, L0604: 1, L0593: 1, L0595: 1, L0601: 1, S0026: 1 and S0384: 1.	AR096: 10, AR039: 4, AR055: 4, AR033: 4, AR053: 3, AR089: 3, AR104: 3, AR052: 2, AR060: 2, AR061: 2	AR096: 14, AR089: 10, AR060: 6, AR061: 6, AR055: 5, AR039: 5, AR052: 4, AR033: 3, AR053: 2, AR104: 2
	Glu-18 to Phe-29, Thr-36 to Pro-45.	Leu-3 to Leu-16, Leu-48 to Phe-58, Gly-113 to Lys-121, Arg-136 to Phe-147, Pro-326 to Ser-346.
	1837	1838
	144 - 452	132 -
	432	433
	839704	839875
	нррні63	HTEPM45
	422	423

																							-						
H0486: 102, S0360: 76,	L0598: 39, H0251: 35,	L0659: 32, H0144: 32,	H0013: 31, H0624: 28,	H0024: 26, H0050: 25,	L0471: 25, L0662: 22,	L0748: 22, H0619: 20,	H0123: 20, S0003: 18,	H0031: 15, H0170: 14,	H0124: 14, H0328: 13,	L0750: 13, H0644: 12,	S0126: 12, S0028: 11,	L0757: 11, S0196: 11,	H0587: 10, S0214: 10,	L0589: 10, S0040: 9,	H0622: 9, L0731: 9, H0171:	8, S0356: 8, L0717: 8,	H0586: 8, H0620: 8, H0252:	8, H0551: 8, H0352: 8,	H0661: 7, H0081: 7, L0747:	7, L0755: 7, S0358: 6,	H0598: 6, L0646: 6, L0771:	6, S3014: 6, H0343: 6,	H0595: 6, S0212: 5, H0329:	5, H0208: 5, H0574: 5,	H0316: 5, H0100: 5, L0666:	5, L0565: 5, H0658: 5,	S0390: 5, S0027: 5, S0011:	5, S0192: 5, S0194: 5,	S0376: 4, H0575: 4, H0039:

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4. H0628: 4. H0090: 4.	UNKWN: 4, L0663: 4,	.0664: 4, S0374: 4, S0380:	4, L0744: 4, S0242: 4,	s, H0645: 3, H0411:	3, H0546: 3, H0012: 3,	S0250: 3, L0768: 3, L0375:	3, H0684: 3, H0672: 3,	, L0754: 3, H0294:	2, H0663: 2, H0592: 2,	S0005: 2, H0333: 2, H0632:	2, H0485: 2, T0060: 2,	H0599: 2, H0309: 2, H0544:	2, H0545: 2, H0041: 2,	H0375: 2, H0553: 2, L0142:	2, H0647: 2, L0776: 2,	.0665: 2, H0648: 2, S0330:	: 2, S0206: 2,	S0032: 2, L0751: 2, H0668:	2, S0384: 2, H0506: 2,	L0615: 1, S0342: 1, H0381:	: 1, S0001: 1,	H0664: 1, H0125: 1, S0354:	1, T0008: 1, H0640: 1,	H0370: 1, H0391: 1, T0039:	1, H0101: 1, H0245: 1,	l, L0021: 1, H0122:	1, H0318: 1, H0231: 1,	H0049: 1, T0003: 1, H0051:	1, H0286: 1, H0364: 1,
4. H0628	UNKWN	L0664: 4	4, L0744	H0295: 3	3, H0546	80250: 3,	3, H0684	80332: 3,	2, H0663	80005: 2,	2, H0485	H0599: 2	2, H0545	H0375: 2	2, H0647	L0665: 2	2, S0378	80032: 2	2, S0384	L0615: 1	1, S0116	H0664: 1	1, T0008	H0370: 1	1, H0101	H0156: 1	1, H0318	H0049: 1	1, H0286
																													-
																							-						

	259-276
	·
H0428: 1, T0023: 1, L0143: 1, H0111: 1, H0163: 1, H0591: 1, H0038: 1, H0616: 1, H0080: 1, L0351: 1, L0564: 1, H0646: 1, H0654: 1, L0763: 1, L0764: 1, L0773: 1, L0648: 1, L0521: 1, L0773: 1, L0522: 1, L0773: 1, L0632: 1, L0522: 1, L0775: 1, L0634: 1, L0526: 1, L0783: 1, L0367: 1, H0659: 1, H0660: 1, H0666: 1, S0118: 1, S0037: 1, H0645: 1, L0693: 1, H0665: 1, H0667: 1, H0665: 1, H0667: 1, H0665: 1, H0667:	Met-1 to Ser-12, AR104: 874, AR060: 684, Asn-23 to Thr-33, AR055: 616, AR033: 568, Asn-35 to Gly-42, Arg-86 to Asp-92, Arg-86 to Arg-86, Arg-86 to Arg-86, Arg-86 to Arg-86, Arg-86 to Arg-86, Arg-86 to Arg-96 to Arg-96. Arg-86 to Arg-96 to Arg-96. Arg-86 to Arg-96 to Arg-96. Arg-86 to Arg-96 to Arg-96. Arg-86 to Arg-96 to Arg-96. Arg-86 to Arg-96 to Arg-96. Arg-86 to Arg-96 to Arg-96. Arg-86 to Arg-96 to Arg-96. Arg-86 to Arg-97. Arg-86 to Arg-97. Arg-86 to Arg-96. Arg-86 to Arg-97. Arg-86 to Arg-97. Arg-86 to Arg-97. Arg-86 to Arg-96. Arg-86 to Arg-97. Arg-98 to Gly-108. Arg-97 to Arg-97. Arg-98 to Gly-108. Arg
	Met-1 to Ser-12, Asn-23 to Thr-33, Asn-35 to Gly-42, Pro-46 to Asp-51, Arg-86 to Asp-92, Ile-98 to Gly-108, Tyr-111 to Phe-128, Asn-140 to Cys-146, Gly-151 to Lys-182, Gly-190 to Ala-196, Leu-200 to Gln-212, Ile-217 to Lys-224,
	1839
	156 - 1244
	434
	839885
·	HTEBP06
	424

	132-148
	17, 16, 113, 113, 12, 8 8 8 8 8 10, 10, 11, 11, 11, 11, 11, 11, 11, 11,
	19, AR052: 17, 17, AR053: 16, 15, AR096: 13, 13, AR104: 12, 10, AR061: 8: 7, S0152: 6, 6, L0777: 6, L080; 8: 4, L0777: 6, L080; 9: 3, L0759: 4, L080; 9: 3, L0759: 4, L080; 2, L0756: 2, S0444: 2, S036; 2, L0756: 2, S0444: 2, S036; 2, L0756: 2, L0756: 2, S003: 1, H0880: 1, H0880: 1, H0880: 1, L0662: 1, L0777: 1, L0662: 1, L0777: 1, L0662: 1, L0777: 1, L0789: 1, S0380: 1, L0777: 1, L0778: 1, L077
	AR039: 19, AR052: 17, AR055: 17, AR089: 15, AR096: 13, AR089: 15, AR096: 13, AR060: 13, AR104: 12, AR033: 10, AR061: 8  L0794: 7, S0152: 6, L0794: 7, S0152: 6, L0757: 4, L0777: 6, L0803: 4, L0777: 6, L0804: 2, L0757: 4, L0759: 4, L0804: 2, S0045: 2, L0756: 2, L0756: 2, L0756: 2, L0756: 2, L0759: 1, H0580: 1, H0041: 1, H0393: 1, H0486: 1, H0575: 1, H0393: 1, H0375: 1, H0580: 1, L0775: 1, L0806: 1, L0775: 1, L0709: 1, L0775: 1, L0709: 1, L0779: 1, L0775: 1, L0709: 1, L0779:
Val-316 to Asn-324	Asn-19 to Pro-28, Ile-45 to Tyr-52.
	1840
	869 - 869
	435
	839888
	HSKY K23
	425

WO 01/90304	
154-171	
AR052: 14, AR053: 8, AR033: 7, AR055: 7, AR104: 7, AR060: 5, AR096: 5, AR089: 4, AR061: 4, AR039: 1 L0777: 8, L0794: 7, L0803: 4, L0748: 4, L0749: 4, L0789: 3, L0759: 3, S0360: 2, H0644: 2, S0422: 2, L0770: 2, L0800: 2, L0766: 2, L0804: 2, L0740: 2, L0750: 2, L0779: 2, L0752: 2, L0755: 2, L0752: 2, L0755: 2, L0753: 1, S0300: 1, H0733: 1, S0300: 1, L0021: 1, H0575: 1, H0412: 1, S0182: 1, H0569: 1, H0090: 1, H0038: 1, H0412: 1, S0440: 1, L0371: 1, L0769: 1, L0761: 1, L0764: 1, L0771: 1, L0521: 1, L0768: 1, L5574: 1, L0783: 1, L0382: 1, L0809: 1,	1, H0547: 1, L0003: 1, H0520. 1, H0547: 1, H0659: 1, H0522: 1, H0134: 1, H0436: 1, H0626: 1, L0747: 1, L0753: 1, L0757: 1, H0444: 1, S0436: 1, S0194: 1,
11 Trp-10 to Gly-16, Ser-19 to Asp-31, Ser-46 to Lys-53, Pro-60 to Ile-78, Ser-85 to Leu-91, Leu-146 to Lys-154, Trp-237 to Arg-246.	
953	
436	
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426 HBUAD85	
426	

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	86-105		·	46-65									28-29								71-88			
							<del></del>		-		<u></u>				· · · · ·									
S0276: 1, H0543: 1 and H0423: 1.	AR089: 1, AR060: 1, AR039: 0, AR104: 0,	AR055: 0, AR053: 0,	AR033: 0	AR039- 35 AR055- 23	033: 19, AR052: 18,	AR053: 17, AR089: 15,	AR060: 12, AR096: 12,	AR104: 11, AR061: 10	H0068: 2, H0619: 1,	H0632: 1, L0471: 1, H0033:	1, H0124: 1, H0316: 1,	.0747: 1 and H0136: 1.	AR096: 5, AR052: 2,	AR089: 2, AR033: 2,	AR061: 2, AR060: 1,	AR104: 1, AR055: 1,	AR053: 0, AR039: 0	H0436: 2, S0354: 1,	C0775: 1, L0658: 1, H0445:	1, H0543: 1 and H0422: 1.	AR052: 4, AR033: 3,	AR053: 3, AR089: 3,	AR060: 2, AR096: 2,	AR055: 2, AR061: 1,
OS HO	Leu-14 to Pro-22, AR Pro-127 to Pro-134, AR		Ser-169 to Gin-203, PAR Leu-273 to Tyr-278. AR	I an 38 to Trn 43 AR			AR	AR	H	HO	1,1	2	Ala-12 to Glu-17, AR	Gly-29 to Arg-35, AR		AF	AF		07	1,	Met-1 to Ala-13, AF		<u>~</u>	2,
g.	1842			1943				_					1844								1845		-	
	777 - 1880			20 241	11. OC								84 - 383								40 - 873			
	437			120	2								439								440			
	840000			040000	000010								840056								840160			
	HCE1N85			TIPO A VOO	CONDAIN								HHETF37								HKAAS52			
	427			90,	470								429								430	!		

	113-143, 62-81	50-66, 178-194, 276-292
Lys-217 to Thr-226. AR039: 0, AR104: 0 H0494: 3, H0559: 2, H0547: 2, L0740: 2, H0423: 2, H0265: 1, H0662: 1, S0348: 1, S0418: 1, H0370: 1, H0492: 1, H0194: 1, H0050: 1, H0006: 1, H0266: 1, L0351: 1, L0766: 1, L0655: 1, S0310: 1, H0689: 1, S0152: 1, H0522: 1, H0543:	AR039: 18, AR033: 12, AR104: 12, AR053: 9, AR052: 9, AR096: 9, AR055: 8, AR089: 8, AR060: 5, AR061: 5 L0741: 3, H0619: 2, T0010: 2, H0539: 2, H0717: 1, L0438: 1, H0435: 1, H0670: 1, H0521: 1, S0436: 1 and H0542: 1.	AR060: 14, AR104: 13, AR033: 11, AR039: 10, AR055: 9, AR089: 8, AR096: 7, AR061: 7, AR053: 6, AR052: 6 L077: 11, L0756: 4, L0596: 4, S0414: 3, H0038:
Lys-217 to Thr-226.	Ser-4 to Arg-13, Pro-15 to Trp-22.	Lys-16 to Leu-21, Glu-70 to Lys-83, Cys-98 to Ser-104, Arg-112 to Glu-118, Lys-155 to Ser-160, Asn-196 to Ser-205, Trp-234 to Ser-241,
<u>'</u>	18	1847
	136 - 747	215 - 1549
		442
	840222	840579
	HISES36	HAPBL12
	431	432

U 01/90304		
		121-137
		i
40: 3, 1: 2, \$0003: 516: 2, 80: 2, 80: 2, 1: 1, \$0001: 20: 1, 1: 1, \$0001: 20: 1, 8: 1, \$1, 49: 1, 6: 1, \$1, 5: 1, \$1, 4: 1, \$1, 6: 1, \$1, 6: 1, \$1, 6: 1, \$1, 728: 1, 8: 1, \$1, 8: 1, \$1,	747: 1, 5: 1 and	033: 11, 053: 8, 104: 7.
3, L0659: 3, L0740: 3, H0265: 2, H0441: 2, S0003: 2, H0032: 2, H0616: 2, L0766: 2, H0144: 2, S0126: 2, L0439: 2, L0780: 2, L0759: 2, S0242: 2, H0542: 2, S0470: 1, S0342: 1, H0650: 1, H0341: 1, S0001: 1, S0282: 1, S0420: 1, S0007: 1, S0476: 1, H0619: 1, T0060: 1, H0013: 1, H0427: 1, H0046: 1, H0024: 1, H0581: 1, S0049: 1, H0553: 1, H0644: 1, H0212: 1, H0634: 1, H0551: 1, L0639: 1, L0772: 1, L0662: 1, L0770: 1, L0769: 1, L0639: 1, L0772: 1, L0663: 1, L0794: 1, L0868: 1, L0805: 1, L0668: 1, H0668: H0547: 1, H0648: 1, H0669:	1, L0754: 1, L0747: 1, L0752: 1, L0755: 1 and L0591: 1.	AR039: 17, AR033: AR096: 8, AR053: AR052: 7, AR104:
Ala-303 to Ala-308, Thr-314 to Gly-321, Asn-349 to Gly-355, Pro-370 to Glu-378, His-384 to Glu-421, Thr-438 to Leu-444.		·
		1848
		330 -
		443
	<u> </u>	840671
1		HTJMJ95
		433

0 01/20004	
	208-229, 235-251
AR089: 7, AR055: 6, AR060: 5, AR061: 5 L0766: 6, L0439: 6, L0749: 5, S0022: 3, H0628: 2, L0769: 2, L0774: 2, L0666: 2, S0152: 2, L0755: 2, H0170: 1, S0476: 1, H0333: 1, H0559: 1, H0270: 1, L0021: 1, H0599: 1, H0123: 1, H014: 1, S0003: 1, H0617: 1, L075: 1, L0637: 1, L0763: 1, L0650: 1, L0763: 1, L0650: 1, L0751: 1, L0747: 1, L0751: 1, L0747: 1, L0751: 1, L0777: 1, L0751: 1,	AR053: 25, AR052: 24, AR055: 16, AR033: 13, AR089: 13, AR096: 12, AR060: 11, AR061: 9, AR104: 8, AR039: 5 L0748: 2, L0779: 2, L0759: 2, H0556: 1, L0534: 1, H0565: 1, H0616: 1, S0422: 1, S0126: 1, L0751: 1, L0749: 1, L0758: 1 and
	Arg-5 to Glu-11.
	1849
	998
	444
	840700
	HTELT78
	434

1, AR039: 1, 0, AR104: 0, 0, AR104: 0, 0, AR104: 0, 0, AR053: 0 4, S0134: 2, 1, S0344: 2, L0803: 1, H0650: 1, 1, H0650: 1, 1, H0561: 1, S0142: 1, L0791: 1, H0547: 1, L0791: 1, H0547: 1, L0792: 1, L0759: 2, AR053: 1, 10, AR089: 10, 9, AR053: 17, 11, AR033: 10, 9, AR104: 9, 8, AR055: 7, 6, AR055: 7, 6, AR055: 7, 6, AR055: 7, 6, AR055: 7,				
HHFBP51 840811 445 100 - 1850 Pro-75 to Lys-91. 690 HHBCS13 840896 446 470 - 1851 Thr-22 to Ser-36. HAJAT72 841335 447 500 - 1852		164-196, 43-75, 91- 113, 138- 156	89-105	79-95
HHFBP51 840811 445 100 - 1850 Pro-75 to Lys-91. 690 HHBCS13 840896 446 470 - 1851 Thr-22 to Ser-36. HAJAT72 841335 447 500 - 1852				
HHFBP51 840811 445 100 - 1850 Pro-75 to Lys-91. 690 HHBCS13 840896 446 470 - 1851 Thr-22 to Ser-36. HAJAT72 841335 447 500 - 1852				
HHFBP51 840811 445 100- 1850 690 HHBCS13 840896 446 470- 1851 HAJAT72 841335 447 500- 1852	L0592: 1.	AR089: 1, AR039: 1, AR055: 0, AR056: 0, AR061: 0, AR104: 0, AR060: 0, AR063: 0 L0774: 4, S0134: 2, H0383: 2, S0344: 2, L0803: 2, S0380: 2, H0650: 1, H0656: 1, S0360: 1, S0222: 1, H0494: 1, H0561: 1, S0142: 1, S0022: 1, S0023: 1, H0594: 1, H0561: 1, L0791: 1, H0547: 1, S0328: 1, H0579: 1, H0579: 1, S0328: 1, H0579: 1, S0328: 1, H0579: 1, L0759: 1 and L0581: 1.	AR096: 10, AR089: 10, AR104: 9, AR039: 9, AR033: 6, AR053: 5, AR060: 5, AR052: 2, AR055: 2, AR061: 2	AR039: 28, AR053: 17, AR096: 11, AR033: 10, AR052: 9, AR104: 9, AR089: 8, AR055: 7, AR060: 6, AR061: 4
HHFBP51 840811 445 100- 1850 690 HHBCS13 840896 446 470- 1851 HAJAT72 841335 447 500- 1852		Pro-75 to Lys-91.	Thr-22 to Ser-36.	
HHFBP51 840811 445 HHBCS13 840896 446 HAJAT72 841335 447		1850		1852
HHFBP51 840811 HHBCS13 840896 HAJAT72 841335		690	470 - 1249	500 - 946
HHFBP51 HHBCS13 HAJAT72			446	447
		840811	840896	841335
		HHFBP51	HHBCS13	HAJAT72
		435	<del></del>	437

	52-71, 90- 106	128-147, 266-282, 29-45
H0561: 1 and S0152: 1.	AR039: 12, AR055: 8, AR083: 7, AR053: 7, AR089: 6, AR052: 6, AR096: 6, AR060: 5, AR061: 4, AR104: 4 L0774: 3, L0783: 3, L0777: 3, H0013: 2, H0024: 2, L0662: 2, L0768: 2, L0565: 2, L0751: 2, L0758: 2, L0603: 2, H0170: 1, S6024: 1, H0661: 1, S0360: 1, S0222: 1, H0370: 1, H0575: 1, H0618: 1, H0545: 1, S0388: 1, H0124: 1, S0440: 1, S0150: 1, S0142: 1, L0770: 1, L0769: 1, L0666: 1, H0547: 1, L0743: 1, L0754: 1, L0749: 1, L0666: 1, H0577: 1, H0506:	AR055: 496, AR039: 256, AR089: 232, AR060: 215, AR033: 209, AR053: 177, AR096: 155, AR052: 154, AR061: 146, AR104: 120 L0439: 5, L0779: 2,
	Glu-12 to Lys-31.	Ser-9 to Ile-16, Asp-110 to Ala-119, Glu-289 to Tyr-294.
	1853	1854
	123 - 476	1475 - 594
	448	449
	842395	843516
	HTLHK92	439 HAGBQ10 843516
	438	439

	64-96, 3- 34, 99- 120, 38-55	21-54, 112-132, 67-89, 92- 108
1156: 7794: 758: 1.	15, 24, 9, 7, 0 0012: nd	, , , , , , , , , , , , , ,
L0777: 2, L0759: 2, H0156: 1, S0010: 1, S0049: 1, H0052: 1, H0328: 1, L0794: 1, L0804: 1, H0144: 1, L0438: 1, L0352: 1, L0758: 1, L0589: 1 and S0412: 1.	AR096: 116, AR053: 115, AR089: 113, AR033: 94, AR052: 89, AR061: 79, AR055: 68, AR060: 67, AR039: 22, AR104: 20 L0794: 4, L0778: 1, T0048: 1, H0327: 1, H0012: 1, H0083: 1, H0038: 1, H0509: 1, L0770: 1, L0769: 1, L0659: 1, L0789: 1 and H0520: 1.	AR089: 5, AR052: 4, AR053: 4, AR096: 3, AR061: 3, AR060: 3, AR104: 1, AR039: 0 L0748: 18, H0547: 8, L0731: 8, H0556: 7, H0039: 6, L0666: 6, H0046: 5, H0059: 5, L0775: 5, L0439: 5, L0755: 5, H0622: 4, L0662: 4, L0740: 4, L0751: 4, L0779: 4, H0575: 3,
	<u> </u>	1856 Pro-55 to Lys-67, A Lys-134 to Glu-144, A Pro-166 to Asn-174, A Pro-192 to Trp-197. A L
	1855	1856
	83 - 520	85 - 678
	450	451
	844034	844529
	HCRBB73	<b>Н</b> WHHU1 1
	044	144

						<del>- ; .</del>																		•••		•••			
H0553: 3, H0529: 3, L0769:	3, L0659: 3, H0519: 3,	L0588: 3, L0608: 3, L0593:	3, S0011: 3, H0255: 2,	S0418: 2, S0046: 2, H0586:	2, S0049: 2, H0150: 2,	H0424: 2, H0644: 2, H0560:	2, H0561: 2, S0002: 2,	S0426: 2, L0763: 2, L0772:	2, L0646: 2, L0655: 2,	L0527: 2, L0518: 2, L0783:	2, L0664: 2, L0665: 2,	L0438: 2, H0689: 2, H0672:	2, H0555: 2, H0631: 2,	S0206: 2, L0752: 2, L0757:	2, L0758: 2, L0485: 2,	L0601: 2, H0543: 2, H0171:	1, H0265: 1, S0040: 1,	H0294: 1, T0049: 1, S0134:	1, H0583: 1, H0657: 1,	H0484: 1, H0661: 1, H0125:	1, S0420: 1, S0354: 1,	S0358: 1, S0360: 1, S0410:	1, H0580: 1, S0132: 1,	H0550: 1, H0431: 1, H0592:	1, H0587: 1, H0333: 1,	H0270: 1, H0013: 1, H0599:	1, T0082: 1, H0318: 1,	H0251:,1, H0309: 1, T0110:	1, H0545: 1, H0041: 1,
																							_						
	-																												
						233															-			_					

WU 01/90304 FC1/03	01/1045
<u> </u>	56-75, 2-
51: 1, H0057: 51: 1, H0358: 1, H0328: 83: 1, 1, H0111: 83: 1, 1, H0551: 50: 1, 1, L0372: 50: 1, 1, L0372: 67: 1, L0372: 67: 1, L0372: 67: 1, L0372: 67: 1, L0372: 84: 1, 1, L0375: 83: 1, L0375: 83: 1, L0375: 83: 1, L0375: 83: 1, L0375: 83: 1, L0375: 83: 1, L0375	42: 1 and 39: 4.
H0620: 1, H0024: 1, H0057: 1, H0014: 1, S0051: 1, H0083: 1, S0024: 1, H0355: 1, H0266: 1, H0271: 1, H0188: 1, S0250: 1, H0328: 1, H0615: 1, L0483: 1, H0674: 1, H0631: 1, H0111: 1, H0062: 1, H033: 1, H0674: 1, H0634: 1, H0551: 1, H0647: 1, H0634: 1, H0551: 1, H0647: 1, H0634: 1, L0456: 1, H0647: 1, H0646: 1, S0144: 1, S0142: 1, S0450: 1, H0647: 1, L0761: 1, L0372: 1, L0658: 1, L0767: 1, L0658: 1, L0678: 1, L0658: 1, L0688: 1, H0659: 1, L0688: 1, H0682: 1, H0684: 1, H0658: 1, H0670: 1, H0696: 1, S0027: 1, L0754: 1, L0759: 1, L0750: 1, L0754: 1, L0759: 1, L0750: 1, L069: 1, S0027: 1, L0759: 1, L0555: 1, L0603: 1, S0106: L0555: 1, L0603: 1, S0106: L0555: 1, L0603: 1, S0106:	1, H0668: 1, H0542: 1 and H0423: 1. AR096: 8, AR039: 4.
ĬĤĬĤĤĤĤĤĤĤĤĤĤĤĤĤĤĤĤĤĤĤĤĤĤĤĤĤ	
	IIe-19 to I.vs-25
· · · · · · · · · · · · · · · · · · ·	1857
	1194 -
	452
	845247
	HRAFR76
	CAA

18	19-37, 88- 106, 40- 56, 62-78, 130-146	110-126,
AR053: 4, AR052: 4, AR089: 3, AR033: 3, AR060: 2, AR104: 2, AR055: 1, AR061: 1 L0756: 4, L0803: 3, L0754: 3, L0731: 3, L0766: 2, L0666: 2, L0779: 2, L0755: 2, S6024: 1, S0114: 1, H0486: 1, L0021: 1, T0082: 1, L0145: 1, L0764: 1, L0363: 1, L0794: 1, L0804: 1, S0052: 1, H0555: 1, L0758: 1, L0592: 1, S0026: 1, H0136: 1 and S0460: 1.	AR051: 2, AR089: 1, AR055: 1, AR052: 1, AR033: 1, AR060: 1, AR096: 1, AR039: 0, AR053: 0, AR104: 0 S0152: 1	AR096: 43, AR053: 36, AR039: 32, AR089: 28, AR052: 26, AR104: 19, AR060: 19, AR033: 18, AR055: 7, AR061: 5 S0360: 3, H0031: 3, H0547: 3, L0015: 2, H0583: 1, L0443: 1, H0613: 1,
·		Gly-44 to Phe-55, Pro-57 to Ser-64, Arg-83 to Gly-90, Leu-98 to Thr-105.
	1858	1859
1517	139 - 612	148 - 546
	453	454
	845355	845465
	HPJA013	HHENF67
	443	44

	91-110	77-94
		120160, 120160, 120160, 120160, 126650, 126650, 129900, 154276, 173360, 173360, 602136, 602136, 602136,
		7q21.3- q22.1
H0586: 1, H0013: 1, S0346: 1, H0546: 1, H0551: 1, H0059: 1, H0509: 1, L0662: 1, L0803: 1, L0774: 1, L0775: 1, L0805: 1, L0657: 1, L0666: 1, L0664: 1, S0380: 1 and H0543: 1.	AR055: 12, AR061: 7, AR060: 6, AR053: 5, AR033: 4, AR089: 4, AR052: 3, AR096: 2, AR104: 2, AR039: 0 H0574: 1 and S0344: 1.	AR055: 4, AR060: 3, AR033: 3, AR096: 3, AR061: 3, AR039: 2, AR089: 2, AR052: 2, AR053: 1, AR104: 1 L0769: 3, L0803: 3, L0748: 3, L0749: 3, H0574: 2, H0046: 2, H0634: 2, S0440: 2, L0794: 2, L0805: 2, L0776: 2, L0439: 2, L0754: 2, L0777: 2, L0755: 2, L0605: 2, L0593: 2, H0686: 1, S0360: 1, L0717: 1, H0069: 1, H0575: 1,
	Met-1 to Ser-7, Gly-16 to Ile-24, Thr-28 to Asp-38, Asp-55 to Phe-64, Ser-76 to Lys-82, Leu-116 to Glu-124.	Gly-49 to Thr-57, Gly-139 to Arg-144.
	1860	1861
	10 - 444	94 - 660
	455	456
	846521	846674
	HLQDC55	HTTJW49
	24	446

	87-111	54-85, 170-198,
		•
1, \$0388: 1, H0510: 1, H0266: 1, H0644: 1, L0455: 1, H0163: 1, H0561: 1, S0438: 1, H0695: 1, L0763: 1, L0800: 1, L0804: 1, L0659: 1, L0775: 1, L0807: 1, L0659: 1, L0783: 1, L0809: 1, L0666: 1, L0665: 1, L0438: 1, H0558: 1, H0539: 1, S0152: 1, H0522: 1, L0740: 1, L0777: 1, L0603: 1, S0276: 1 and H0542: 1.	AR089: 2, AR096: 2, AR053: 2, AR052: 2, AR039: 2, AR060: 1, AR055: 1, AR104: 1, AR033: 1, AR061: 1 L0766: 6, L0749: 6, L0803: 2, H0395: 1, H0556: 1, H0599: 1, H0599: 1, H0599: 1, L0772: 1, L0800: 1, L0772: 1, L0806: 1, L0382: 1, S0152: 1, L0750: 1, L0608: 1, H0542: 1 and H0543: 1.	AR089: 2, AR096: 2, AR039: 2, AR033: 2,
	Gln-33 to Gly-42, Ser-69 to Ala-77.	Gln-87 to Pro-104, Trp-107 to Lys-119,
	1862	1863
	98 - 442	32 - 997
	457	458
	846772	847144
	HSYAD28	HLWAR77
	744	448

WO 01/90304																	PC.	17U	<b>S</b> 0:	1/16	450
121-141, 21-45, 208-224	47-77																				
												•						- 400		_	
00: 1, 33: 1, 55: 1 7759: 2.	)61: 203, )33: 175,	55: 147,	89: 92, 52: 66	6: 10,	6, L0748:	1/: 5, 5 UDS42.	3; 4,	4, L0666:	51: 4,	4, L0759:	5: 4,	3, H0484:	6: 3,	3, H0050:	37: 3,	3, L0770:	2: 3,	3, L0497:	9:3,	3, L0740:	6: 2,
AR104: 1, AR060: 1, AR061: 1, AR053: 1, AR052: 1, AR055: 1 H0553: 4 and L0759: 2.	AR104: 249, AR061: 203, AR060: 179, AR033: 175,	AR039: 168, AR055: 147,	AR096: 122, AR089: 92, AR053: 67, AR052: 66	L0741: 18, L0766: 10,	L0438: 9, H0052: 6, L0748:	6, H0622: 5, H0617: 5, r occs: s H0520: s HC	5, S0418: 4, H0553: 4,	H0059: 4, H0494: 4, L0666:	4, H0521: 4, L0751: 4,	L0750: 4, L0758: 4, L0759:	4, L0593: 4, L0595: 4,	H0543: 4, H0656: 3, H0484:	3, S0420: 3, H0706: 3	H0086: 3, H0009: 3, H0050:	3, H0124: 3, H0087: 3,	T0042: 3, H0509: 3, L0770:	3, L0761: 3, L0772: 3,	L0771: 3, L0768: 3, L0497:	3, L0776: 3, L0659: 3,	L0664: 3, L0439: 3, L0740:	3, L0591: 3, H0556: 2,
Thr-156 to Gln-163, Ser-168 to Lys-173, Glu-240 to Phe-246, Ser-285 to His-291, Tyr-297 to Gln-306, Glu-312 to Ser-320.	His-78 to Tyr-106, Glu-115 to Asp-120,	Trp-139 to Thr-146,	Pro-153 to Inr-187, Pro-213 to Ser-220.																		
	1864	. ,							_												
	1134 -									•											
	459								•	<u> </u>		_									
	847388													-							
	HCE2W33																				
	449		,																		

																_				-									
									_																				
2, S0442:	0: 2,	2, H0333:	15: 2,	2, H0292:	15: 2,	2, L0533:	6: 2,	2, L0809:	17: 2,	2, S0028:	2: 2,	2, H0136:	24: 1,	1, H0222:	6: 1,	1, H0341:	5: 1,	1, H0676:	08: 1,	1, H0645:	57: 1,	1, H0632:	75: 1,	1, H0318:	35: 1,	1, H0012:	24: 1,	1, T0010:	88: 1,
S0212: 2, H0661: 2, S0442:	2, S0358: 2, S0360: 2,	H0393: 2, S0278: 2, H0333:	2, H0544: 2, H0545: 2,	H0046: 2, H0041: 2, H0292:	2, S0036: 2, H0135: 2,	H0100: 2, L0764: 2, L0533:	2, L0499: 2, L080	L0655: 2, L0382: 2, L0809:	2, S0374: 2, H054	H0435: 2, H0436: 2, S0028:	2, L0747: 2, L0752: 2,	L0755: 2, L0757:	2, L0411: 1, H0624: 1,	H0265: 1, T0002: 1, H0222:	1, S0040: 1, H0716: 1,	H0650: 1, H0657: 1, H0341:	1, S0282: 1, H0255: 1	H0125: 1, S0376: 1, H0676:	1, H0580: 1, H020	S0045: 1, S0476:	1, L0717: 1, H0437: 1,	H0586: 1, H0497: 1, H0632:	1, H0349: 1, H057	H0618: 1, H0253: 1, H0318:	1, H0421: 1, H0235: 1,	H0572: 1, H0571: 1, H0012:	1, H0197: 1, H0024: 1,	H0373: 1, H0051: 1, T0010:	1, H0594: 1, H0288: 1,
				•						_				•															
																										-			

VO 01/90304	PC1/0501/10450
	1-28, 151- 175, 127- 143
H0328: 1, H0428: 1, L0142: 1, S0364: 1, H0040: 1, H0616: 1, H0551: 1, H0264: 1, H0268: 1, H0412: 1, T0041: 1, S0440: 1, S0144: 1, S0142: 1, S0210: 1, H0695: 1, L0369: 1, L0763: 1, L0769: 1, L5565: 1, L0774: 1, L0646: 1, L0643: 1, L0678: 1, L0649: 1, L0658: 1, L0383: 1, L0663: 1, H0519: 1, H0658: 1, H0670: 1, H0648: 1, H0696: 1, H0134: 1, H0555: 1, H0576: 1, S3014: 1, S0032: 1, L0731: 1, H0445: 1, S0434: 1, L0781: 1, H0445: 1, L0469: 1, H0668: 1, S0276: 1, L0469: 1, H0672: 1 and S0460: 1	Ala-118 to Phe-124, AR096: 2, AR033: 2, Arg-178 to Lys-201. AR053: 2, AR060: 2, AR089: 1, AR104: 1, AR052: 1, AR055: 1, AR061: 1, AR059: 0 S0358: 36, S0374: 19, S0408: 16, S0444: 15, L0518: 12, S0442: 11,
	1865 A
	619 - 11
	460
	847431
	HSOAC39
	450

10 01/20304			1 0 17 0 50 17 10 45 0
		40-56	
			·
1, L0640: 1, L0763: 1, L0642: 1, L0363: 1, L0386: 1, L0803: 1, L0774: 1, L0775: 1, L0805: 1, L0776: 1, L0659: 1, L0517: 1, L0543: 1, L0664: 1, L0665: 1, H0144: 1, H0682: 1, H0658: 1, H0670: 1, S0380: 1, S0044: 1, H0134: 1	1, 204: 1, L0743: 1, L0750: 1, L0731: 1, L0757: 1, H0445: 1, S0011: 1, H0668: 1 and S0276: 1.	AR035: 2, AR035: 2, AR039: 2, AR033: 2, AR089: 1, AR052: 1, AR061: 1, AR060: 1, AR096: 0 H0255: 4, H0617: 3, L0666: 3, H0690: 3, L0742: 3, S0222: 2, H0618: 2, L0665: 2, H0265: 1, H0556:	1, H0295: 1, S0212: 1, H0661: 1, S0354: 1, S0376: 1, S0360: 1, S0046: 1, H0619: 1, L0717: 1, S0278: 1, H0455: 1, H0438: 1, H0559: 1, S0049: 1, H0052: 1, H0024: 1, S0051: 1, S6028: 1, H0428: 1, H0424:
		Ala-28 to 1 nr-33.	
		1800	
		707	
		461	
		84/551	
		HAJAVUI	
		164	

	93-114, 17-35, 70- 86
1, H0673: 1, H0124: 1, H0087: 1, H0551: 1, H0561: 1, S0210: 1, H0529: 1, L0761: 1, L0644: 1, L0803: 1, L0774: 1, L0775: 1, L0805: 1, L0656: 1, H0519: 1, H0659: 1, H0672: 1, L0777: 1, L0698: 1 and H0677: 1,	AR053: 1, AR089: 1, AR033: 1, AR061: 1, AR060: 0, AR096: 0, AR052: 0, AR055: 0, AR039: 0, AR104: 0 L0805: 3, L0659: 3, S0406: 3, L0779: 3, S0376: 2, H0013: 2, H0553: 2, L0761: 2, L0773: 2, L0662: 2, L0794: 2, L0803: 2, L0665: 2, H0539: 2, S0404: 2, L0748: 2, L0754: 2, L0731: 2, H0565: 1, S0114: 1, H0583: 1, H0650: 1, S0212: 1, S0442: 1, S0354: 1, S0408: 1, H0351: 1, H0592: 1, H0575: 1, S0474: 1, S0408: 1, H0575: 1, S0474: 1, H0581: 1, H0522: 1, S0382: 1, S0448: 1, H0529: 1, L0640: 1, L0763: 1, L0764:
1, 1 H0 1, 5 L0 L0 H0 H0	Lys-53 to Asn-58. ARARAR ARAR ARAR ARAR ARAR ARAR ARAR
	1867
	522
	462
	847568
	452 HWGQC67
	452

	46-62, 18- 34	04-80
1, L0771: 1, L0804: 1, L0776: 1, L0655: 1, L0788: 1, L0666: 1, H0666: 1, H0555: 1, L0751: 1, L0750: 1 and L0759: 1.	AR052: 7, AR096: 7, AR089: 5, AR053: 4, AR060: 4, AR033: 3, AR104: 2, AR061: 2, AR055: 2, AR039: 0 H0438: 1, L0764: 1, L0626: 1, H0445: 1 and S0194: 1.	AR096: 3, AR089: 2, AR053: 1, AR104: 1, AR055: 1, AR060: 1, AR052: 1, AR061: 1, AR039: 0, AR033: 0 L0439: 11, L0751: 5, S0222: 3, L0769: 3, L0766: 3, H0617: 2, S0038: 2, L0770: 2, L0764: 2, L0794: 2, L0438: 2, L0747: 2, L0752: 2, H0445: 2, S6024: 1, S0001: 1, H0351: 1, H0586: 1, S0010: 1, H0373: 1, S0051: 1, T0010: 1, S6028: 1, H0264: 1, S0150: 1, L0768: 1, S0052: 1,
	Ser-35 to Arg-45.	Pro-3 to Glu-8.
	1868	1869
	394 - 726	709 - 1014
	463	464
	847634	847677
	HFIJC17	HBXCD74
	453	454

		210-235,	95-117,	184-204,	161-177,	123-139														_	***************************************							
					···									_														
H0522: 1, L0741: 1, L0753:	1, L0758: 1 and H0422: 1.	AR033: 5, AR096: 5,	AR052: 5, AR055: 5,	AR089: 4, AR053: 4,	AR061: 4, AR060: 4,	AR039: 2, AR104: 2	L0748: 8, L0766: 7,	L0771: 5, S0422: 3, H0529:	3, H0519: 3, L0749: 3,	L0756: 3, H0641: 2, L0659:	2, S0374: 2, L0438: 2,	H0547: 2, L0751: 2, L0750:	2, L0758: 2, H0484: 1,	S0420: 1, S0442: 1, S0358:	1, S0410: 1, S0007: 1,	H0632: 1, L0483: 1, H0606:	1, H0268: 1, H0494: 1,	S0150: 1, L0763: 1, L0637:	1, L0764: 1, L0768: 1,	L0774: 1, L0653: 1, L0809:	1, L0666: 1, H0144: 1,	H0520: 1, H0658: 1, S0328:	1, H0539: 1, S0406: 1,	S0027: 1, L0744: 1, L0754:	1, L0777: 1, S0434: 1,	L0592: 1, L0608: 1, L0593:	1, H0136: 1, H0543: 1 and	H0422: 1.
		Pro-44 to Trp-49,	Met-58 to His-65,	Pro-68 to Lys-76,	Ser-153 to Asp-158,	Ser-235 to Gln-246.							<del></del>			:												
		1870																										
		1284 -	<del>24</del>																									
		465	_																					-				
		847876															_				_							
		HPICD14																										
		455																										

848184 466 21 - 521 1871 Glu-151 to Gln-157, AR096. 1, AR039: 1, AR060. 1, AR052. 1, AR069. 2, AR069. 1, AR069. 2, AR069. 3, A
466 21 - 521 1871 Glu-151 to Gln-157.  467 299 - 1872 Gln-10 to Tyr-16, 640 Asn-20 to Arg-25.  468 652 - 1873
466 21 - 521 1871 Glu-151 to Gln-157.  467 299 - 1872 Gln-10 to Tyr-16, 640 Asn-20 to Arg-25.  468 652 - 1873
466 21 - 521 1871 Glu-151 to Gln-157.  467 299 - 1872 Gln-10 to Tyr-16, 640 Asn-20 to Arg-25.  468 652 - 1873
466 21 - 521 1871 Glu-151 to Gln-157.  467 299 - 1872 Gln-10 to Tyr-16, 640 Asn-20 to Arg-25.  468 652 - 1873
466 21 - 521 1871 Glu-151 to Gln-157. 467 299 - 1872 Gln-10 to Tyr-16, 640 Asn-20 to Arg-25. 468 652 - 1873 1053
466 21 - 521 - 467 299 - 640 468 652 - 1053
1184
848184
HBGNJ21 HBGNW78 HSDZN36
456 457 I

	32.48, 98- 117, 8-24	88-107
·		
S0408: 1, H0728: 1, L0717: 1, H0351: 1, S0222: 1, H0455: 1, H0574: 1, H0615: 1, H0646: 1, H0615: 1, H0648: 1, H0659: 1, H0628: 1, H0690: 1, H0591: 1, H0623: 1, S0440: 1, L0637: 1, L0771: 1, L0794: 1, L0774: 1, L0805: 1, L0667: 1, L0659: 1, L0668: 1, L0668: 1, L0668: 1, H0519: 1, H0658: 1, S0378: 1, H0518: 1, S0152: 1, H0521: 1, S3012: 1, L0779: 1, L0752: 1, L0759: 1, L0753: 1, L0759: 1, L0753:	AR039: 74, AR096: 66, AR053: 44, AR055: 38, AR052: 38, AR033: 34, AR104: 33, AR089: 27, AR060: 21, AR061: 19	AR039: 16, AR055: 12, AR104: 8, AR053: 8, AR033: 8, AR060: 7, AR052: 7, AR096: 6, AR089: 6, AR061: 6
		Glu-9 to Leu-18, Leu-22 to Pro-27.
	1874	1875
	9 - 401	301 - 795
	469	470
•	848480	848610
	HFPCS09	HAIBB95
	459	460

	61-79	110-128	2-24, 116- 139, 32- 49, 93- 111, 62-78
H0038: 3, L0770: 3, L0777: 3, L0794: 2, L0766: 2, L0803: 2, L0779: 2, L0758: 2, S0132: 1, H0393: 1, H0549: 1, H0586: 1, H0559: 1, H0004: 1, H0581: 1, H0545: 1, H0457: 1, H0266: 1, H0030: 1, H0316: 1, H0551: 1, H0056: 1, L0659: 1, L0517: 1, L0792: 1, H0691: 1, H0555: 1 and L0599: 1.	AR096: 1, AR089: 1, AR060: 1, AR061: 1, AR033: 0, AR052: 0, AR055: 0, AR039: 0, AR053: 0, AR104: 0 H0561: 1, L0748: 1 and H0542: 1.	AR089: 1, AR033: 0, AR055: 0, AR039: 0, AR053: 0, AR060: 0, AR096: 0, AR061: 0, AR052: 0, AR104: 0 H0013: 1 and H0561: 1.	AR096: 6, AR089: 4, AR039: 3, AR053: 3, AR033: 3, AR052: 3, AR060: 2, AR104: 2,
	1876 Gly-82 to Tyr-87.	Ala-57 to Trp-62.	Arg-26 to Cys-31.
	1876	2 1877	1878
	417	10 - 432	158 -
	471	472	473
	848769	848773	848785
	ннея08	HE8OM63	HAJAG88
	461	462	463

	<del></del>
	739-756, 89-105, 249-265, 166-182, 511-527
AR055: 2, AR061: 1 L0527: 2, H0657: 1, H0341: 1, S0222: 1, H0438: 1, T0048: 1, S0049: 1, S0250: 1, S0036: 1, H0087: 1, H0561: 1, L0369: 1, L0388: 1, L0518: 1, H0520: 1, H0519: 1, H0435: 1, L0366: 1 and L0697: 1.	177777 HOHAHOHOHHHHH
	Lys-136 to Glu-143, Lys-184 to Ser-189, Ser-195 to Asn-205, Asn-232 to Thr-240, Arg-276 to Phe-285, Glu-406 to Glu-414, Thr-476 to Tyr-482, Tyr-496 to Ala-501, Pro-588 to Glu-593, Pro-612 to Leu-618, Gly-623 to Glu-593, Thr-670 to Ser-681, Lys-701 to Glu-715, Lys-773 to Asn-797, Ser-809 to Asp-823.
	1879
	33 - 2522
	474
	849547
	HAJCL92
	464

	109-133, 175-191, 30-46
1, H0013: 1, H0069: 1, H0575: 1, H0004: 1, H0318: 1, H0050: 1, H0014: 1, S0388: 1, H0687: 1, S0250: 1, S0003: 1, H0090: 1, H0616: 1, L0060: 1, H0551: 1, H0268: 1, H0412: 1, H0413: 1, H0561: 1, S0352: 1, S0372: 1, S0150: 1, L0640: 1, L0804: 1, L0650: 1, L0383: 1, L0791: 1, H0144: 1, H0519: 1, H0435: 1, H0648: 1, H0672: 1, H0521: 1, S0406: 1, H0478: 1, S0037: 1, S0027: 1, L0439: 1, L0751: 1, L0754: 1, L0750: 1, L0752: 1, L0759: 1, L0361: 1, H0136: 1 and S0196: 1.	AR096: 2, AR104: 1, AR055: 1, AR033: 1, AR061: 1, AR060: 1, AR089: 1, AR039: 0, AR052: 0, AR053: 0 S0358: 6, L0803: 5, H0510: 2, S0438: 2, S0422: 2, L0769: 2, L0805: 2, L0527: 2, L0789: 2, L0748: 2, L0747: 2, L0750: 2, L0615: 1, L0460: 1, H0484:
·	
	62 - 646 1880
	15 849576 475
	465 HHAMA15

	245-261	298-314, 69-85
1, S0444: 1, S0222: 1, H0486: 1, T0048: 1, H0041: 1, H0024: 1, H0646: 1, L0800: 1, L0662: 1, L0629: 1, L0518: 1, L0809: 1, L0791: 1, S0374: 1, H0627: 1, L0756: 1, L0755: 1, L0731: 1 and L0759: 1.	AR096: 3, AR089: 3, AR053: 3, AR060: 2, AR033: 2, AR104: 2, AR055: 2, AR039: 1, AR052: 1, AR061: 1 H0436: 3, L0605: 3, H0551: 2, L0662: 2, S0028: 2, L0748: 2, L0754: 2, L0759: 2, S0134: 1, S0001: 1, S0358: 1, S0360: 1, H0550: 1, H0404: 1, H0156: 1, H0031: 1, H0591: 1, S0386: 1, L0521: 1, L0803: 1, H0547: 1, H0682: 1, H0658: 1, S0152: 1, S0027: 1, L0745: 1, H0445: 1, S0196: 1 and H0423: 1.	AR033: 7, AR060: 7, AR052: 7, AR055: 6, AR096: 5, AR089: 5,
	Ala-5 to Asn-28, Pro-47 to His-52, Tyr-83 to Arg-90.	Met-1 to Ser-8, Ser-31 to Asp-40, Asn-44 to Val-51,
	1881	1882
	1353	179 - 1405
	476	477
	849610	849645
	HPJDE45	HPMJG77
	466	467

									-																
Asp-87 to Ser-95, AR053: 5, AR039: 4,	5, /			(.,	CA	2, L0809; 2, H0436; 2,	L0747: 2, L0750: 2, L0755:	2, H0624: 1, S0418: 1,	H0741: 1, S0132: 1, H0331:	1, H0013: 1, H0318: 1,	S0049: 1, H0052: 1, H0596:	1, H0457: 1, H0051: 1,	H0510: 1, S6028: 1, S0214:	1, H0428: 1, H0553: 1,	H0644: 1, H0032: 1, H0090:	1, H0591: 1, H0616: 1,	H0413: 1, H0494: 1, L0475:	1, S0438: 1, S0344: 1,	L0796: 1, L0637: 1, L0646:	1, L0800: 1, L0648: 1,	L0804: 1, L0806: 1, L0776:	1, L0655: 1, L0807: 1,	L0527: 1, L0659: 1, L0790:	1, L0791: 1, L0664: 1,	H0725: 1, S0148: 1, H0520:
					-																				

	130-146
1, H0519: 1, H0593: 1, S0330: 1, H0521: 1, H0522: 1, S0406: 1, S0392: 1, S3014: 1, S0028: 1, S0206: 1, L0740: 1, L0754: 1, L0745: 1, L0779: 1, L0777: 1, L0752: 1, L0731: 1, S0436: 1, L0596: 1, S0194: 1 and H0423: 1.	AR052: 20, AR096: 20, AR089: 15, AR053: 14, AR060: 13, AR033: 10, AR055: 9, AR039: 8, AR104: 5, AR061: 4 S0126: 6, L0766: 5, S0046: 3, S0152: 3, L0748: 3, S0354: 2, S0376: 2, S0045: 2, H0013: 2, H0550: 2, H0634: 2, H0547: 2, H0521: 2, S0028: 2, L0747: 2, L0731: 2, L0596: 2, S0040: 1, H0657: 1, H0381: 1, S0356: 1, S0360: 1, H0393: 1, L0717: 1, H0370: 1, H0599: 1, H0318: 1, H0581: 1, H0123: 1, L0471: 1, H0024: 1, H0014: 1, H0266: 1, S0003: 1, S0022: 1, H0031: 1, H0591: 1, H0038:
·	Pro-3 to Thr-9, Leu-39 to Val-44, Ile-121 to Tyr-128, Ser-149 to Val-156.
	1883
	184 - 723
	478
	850225
	468 HBCCG79
	468

	95-111	159-179	234-251, 18-34,
0529: 0659: 0555: 0653:	1, 1, 1, 10657: 10591: 10522:	6, 4, 4, 6, 6, 1. 1.	4,4
H0561: 1, S0144: 1, H0529: 1, L0646: 1, L0794: 1, L0774: 1, L0776: 1, L0659: 1, L0666: 1, L0664: 1, H0435: 1, S0378: 1, H0555: 1, S0207: 1, S0206: 1, L0750: 1, L0759: 1, H0653: 1 and H0543: 1.	AR033: 1, AR096: 1, AR052: 1, AR055: 1, AR060: 1, AR089: 1, AR104: 1, AR039: 1, AR061: 1, AR053: 1 H0656: 2, S0420: 2, L0364: 2, H0650: 1, H0657: 1, S0356: 1, S0360: 1, H0486: 1, H0598: 1, H0591: 1, H0529: 1, L0764: 1, H0519: 1, H0521: 1, H0522: 1, S0044: 1, H0445: 1, S0194: 1 and H0677: 1.	AR055: 8, AR061: 5, AR060: 5, AR096: 4, AR089: 4, AR052: 4, AR053: 3, AR104: 3, AR039: 3 H0623: 2 and S0278: 3	AR089: 4, AR033: AR052: 4, AR096:
	1884 Thr-43 to Leu-48, Ala-74 to Ser-85, Ser-122 to Asn-130, Gln-133 to Gly-139.	Ala-47 to Asp-53, Glu-105 to Arg-112, Tyr-150 to Leu-157.	1886 Gly-38 to Asp-47, Thr-208 to Phe-221,
	1884	1885	1886
	19 - 651	367 - 960	3238 - 1439
	479	480	481
	850238	850252	850353
	нгінQ53	HUVFU38	471 HUDBK83
	469	470	471

157-173,	443-459																												
		<del>,, ,, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,</del>						. <del>-</del>																					
AR053: 3, AR060: 3,	AR061: 3, AR055: 3,	AR039: 2, AR104: 2	H0253: 10, H0617: 8,	H0559: 7, H0265: 6, H0618:	5, H0551: 5, S0434: 5,	H0052: 4, H0620: 4, L0794:	4, H0556: 3, H0135: 3,	H0087; 3, L0659; 3, L0666;	3, L0663: 3, L0438: 3,	H0522: 3, L0749: 3, H0171:	2, H0657: 2, H0341: 2,	H0484: 2, H0255: 2, S0356:	2, S0360: 2, S0046: 2,	H0550: 2, H0251: 2, H0051:	2, H0188: 2, H0424: 2,	H0031: 2, H0040: 2, H0494:	2, S0344: 2, L0769: 2,	.0662: 2, L0774: 2, L0783:	, L0809: 2, H0696: 2,	,0439: 2, L0751: 2, L0779:	2, L0731: 2, L0759: 2,	.0605: 2, L0361: 2, L0601:	2, H0624: 1, H0159: 1,	S6024: 1, H0295: 1, H0656:	1, S0420: 1, S0442: 1,	S0408: 1, H0637: 1, L0717:	1, H0351: 1, S0222: 1,	H0441: 1, H0370: 1, H0592:	1, H0586: 1, H0497: 1,
Glu-273 to Tyr-279, A			Ser-365 to Leu-370, I				4	<u> </u>	3,	<u>H</u>	- 6	<u>H</u>		<u>H</u>	<u>~</u>	<u> </u>	<u>~</u>	<u> </u>		7	<u>, 2</u>	<u> </u>	<u> </u>	<u>×</u>		<u>S</u>	<u></u>	<u> </u>	1,
																							_						
				_																									

L0750: 1, L0755: 1, L0757: 1, L0758: 1, S0031: 1, S0436: 1, L0593: 1, H0667: 1, H0217: 1, H0423: 1, H0422: 1 and S0042: 1. AR052: 5, AR039: 4, AR053: 4, AR039: 2, AR055: 3, AR060: 3, AR055: 3, AR060: 3, AR055: 3, AR060: 3, AR055: 3, AR069: 2, AR104: 2, AR061: 1 H0521: 7, L0519: 4, L0598: 3, L0794: 3, L0779: 3, L0755: 3, H0542: 3, H0637: 2, H0436: 2, L0743: 2, L0749: 2, L0752: 2, L0809: 2, H0436: 2, L0743: 2, L0631: 1, H0486: 1, H0014: 1, H0486: 1, H0014: 1, H0486: 1, H051: 1, S0144: 1, S0344: 1, L0631: 1, L0800: 1, L0631: 1, L0800: 1, L0631: 1, L0776: 1, L0557: 1, H0478: 1, L0666: 1, H0144: 1, H0672: 1, H0561: 1, H0478: 1, L0756: 1, H0756: 1,
L0750: 1, L0755: 1, L0757: 1, L0758: 1, S0031: 1, S0436: 1, L0593: 1, H0667: 1, H0217: 1, H0423: 1, H0422: 1 and S0042: 1, AR052: 5, AR039: 4, AR053: 4, AR033: 3, AR055: 3, AR060: 3, AR055: 3, AR060: 3, AR055: 3, AR069: 2, AR104: 2, AR061: 1 H0521: 7, L0519: 4, L0598: 3, L0794: 3, L0752: 2, L0749: 2, L0752: 2, L0749: 2, L0752: 2, L0749: 2, L0752: 2, L0599: 2, H0549: 2, H0661: 1, H0305: 1, S0358: 1, S0360: 1, S0278: 1, H0309: 1, H0304: 1, H0309: 1, H0014: 1, H0309: 1, H0304: 1, L0651: 1, L0806: 1, L0651: 1, L0806: 1, L0657: 1, L0659: 1, L0666: 1, H0144: 1, H0750: 1, H056: 1, H0478: 1, L0750: 1, H056: 1, H0478:
L0750: 1, L0755: 1, L0757: 1, L0758: 1, S0031: 1, S0436: 1, L0593: 1, H0667: 1, H0217: 1, H0423: 1, H0422: 1 and S0042: 1. AR052: 5, AR039: 4, AR053: 4, AR033: 3, AR096: 3, AR060: 3, AR096: 3, AR060: 3, AR096: 3, L0799: 2, AR104: 2, AR061: 1 H0521: 7, L0519: 4, L0598: 3, L0794: 3, L0779: 3, L0755: 3, H0542: 3, H0667: 2, H0541: 2, L0662: 2, L0803: 2, H04936: 2, L0749: 2, L0752: 2, L0752: 2, L0809: 2, H0543: 1, H0661: 1, H0305: 1, S0358: 1, S0360: 1, R0427: 1, T0082: 1, H0309: 1, H0014: 1, H0271: 1, H0561: 1, S0144: 1, L0806: 1, L0657: 1, L0659: 1, L0666: 1, H0144: 1, H0672: 1, H0696: 1, H0478: 1, L0760: 1, L0567: 1, L0756: 1
L0750: 1, L0755: 1, L0757: 1, L0758: 1, S0031: 1, S0436: 1, L0593: 1, H0667: 1, H0217: 1, H0423: 1, H0422: 1 and S0042: 1. AR052: 5, AR039: 4, AR053: 4, AR033: 3, AR096: 3, AR060: 3, AR104: 2, AR061: 1 H0521: 7, L0519: 4, L0598: 3, L0794: 3, L0779: 3, L0755: 3, H0542: 3, H0637: 2, H0251: 2, L0662: 2, L0803: 2, H0436: 2, L0743: 2, L0749: 2, L0752: 2, L0803: 2, H0436: 2, H0661: 1, H0305: 1, S0358: 1, S0360: 1, S0278: 1, H0486: 1, H0427: 1, T0082: 1, L0800: 1, L0804: 1, L0651: 1, L0806: 1, L0651: 1, L0776: 1, L0527: 1, L0659: 1, L0666: 1, H0144: 1, H0672: 1, H0696: 1, H0478:
L0750: 1, L0758: 1, S06 S0436: 1, L0595 S0436: 1, L0595 1, H0217: 1, H0 H0422: 1 and St AR052: 5, AR AR053: 4, AR AR053: 4, AR AR053: 3, AR AR055: 3, AR AR057: 2, H025 L0598: 3, L0749 2, L0803: 2, H0 L0743: 2, L0749 2, L0599: 2, H0 H0661: 1, H030 1, S0344: 1, L06 L0800: 1, L0806 1, L0806: 1, L06 L0776: 1, L0527 1, L0666: 1, H0 H0672: 1, H069 1, L0666: 1, H069 1, L0666: 1, H069 1, L0666: 1, H069
<i>F</i> :
188
38 - 391
482
850581
HDPSB01
472

	131-147	66-90, 1- 19, 36-54, 97-113	93-111
1, H0445: 1, H0595: 1, L0592: 1, S0192: 1 and S0242: 1.	AR033: 12, AR104: 12, AR060: 9, AR089: 8, AR055: 7, AR061: 7, AR053: 6, AR052: 6, AR039: 4, AR096: 4 H0624: 2, H0014: 2, H0622: 2, H0038: 2, H0616: 2, H0661: 1, T0082: 1, H0494: 1, H0538: 1, H0144: 1, S0126: 1, L0743: 1, L0754: 1 and L0758: 1.	AR055: 6, AR096: 6, AR052: 5, AR060: 4, AR089: 4, AR033: 3, AR039: 3, AR061: 3, AR053: 2, AR104: 1 H0457: 4, S0045: 1, H0586: 1, H0581: 1, H0266: 1, H0628: 1, L0659: 1 and H0519: 1.	AR052: 10, AR053: 10, AR055: 9, AR033: 6, AR061: 5, AR060: 5, AR039: 5, AR089: 5, AR104: 4, AR096: 4 S0420: 1, H0424: 1,
	1888 Pro-16 to Thr-25, Thr-47 to Leu-54, Tyr-62 to Gln-77, Pro-112 to Tyr-131.	1889 Leu-32 to Val-37.	1890 Glu-8 to Thr-13, Glu-18 to Pro-25, Ser-48 to Val-55.
	· · · · · · · · · · · · · · · · · · ·	1889	1890
	45 - 572	- 427 - 831	230 - 691
	483	484	485
	850629	850930	850963
	HKAPB61	HMEGF05	475. HPTVF17
	473	474	475.

	133-165,	1-22, 57-	75, 92-108																						56-74			
											·									- 1,	<del></del>							
S0144: 1 and L0595: 1.	1		AR055: 5, AR039: 5,	AR060: 4, AR096: 4,	AR061: 3, AR104: 3	L0157: 4, H0038: 4,	H0013: 3, L0766: 3, S0354:	2, H0545: 2, L0794: 2,	L0783: 2, L0665: 2, H0144:	2, L0756: 2, L0777: 2,	L0593: 2, L0595: 2, H0665:	2, H0656: 1, H0484: 1,	H0254: 1, H0125: 1, S0356:	1, S6026: 1, H0485: 1,	H0618: 1, H0318: 1, S0388:	1, H0266: 1, H0039: 1,	H0673: 1, H0412: 1, L0770:	1, L0769: 1, L0761: 1,	L0803: 1, L0653: 1, L0382:	1, L0792: 1, S0052: 1,	H0690: 1, H0658: 1, H0539:	1, S3014: 1, S0028: 1,	L0779: 1, L0758: 1 and	L0759: 1.	AR052: 11, AR055: 9,		AR033: 6, AR096: 6,	
	1891 Glu-40 to Gln-48.																								Ser-31 to Gln-44,	Ser-91 to Gln-96.		
	1891											_					-								1892			
	19 - 561																								1129 -	1530		
	486																								487			
	851303				-																				851311			
	HDLBF57	•																•				-			HE8QT62	,		
	476																								477			

	3-27, 93- 118, 32- 49, 73-89	
0032: 0593: nnd	od , , ,	7, 6, 5, 3 10634: 1, 10144:
AR039: 2 H0090: 2, 0144: 2, H0 S0418: 1, 0580: 1, S0 H0244: 1, H0039: 1, H0 , H0063: 1, 0529: 1, L0 , L0790: 1, H0543: 1 a	AR055: 7, AR052: 4, AR053: 4, AR061: 4, AR033: 3, AR089: 3, AR096: 3, AR104: 3, AR039: 2 L0749: 2, H0144: 1 and 0748: 1.	9, AR052: 7, 6, AR053: 6, 5, AR061: 5, 3, AR104: 3, 2, L0779: 2, 1, S0442: 1, H063: 1, L0809: 1, H0
AR104: 3, AR039: 2 H0013: 3, H0090: 2, S0002: 2, H0144: 2, H0161: 1, S0134: 1, S0418: 1, S0360: 1, H0580: 1, S0045: 1, S0222: 1, H0244: 1, H0575: 1, H0039: 1, H0032: 1, H0616: 1, H0063: 1, S0142: 1, H0529: 1, L0372: 1, L0803: 1, L0790: 1, L0791: 1, H0521: 1, L0593: 1, S0242: 1, H0543: 1 and H0423: 1.	AR055: 7, AR053: 4, AR061: 4, AR089: 3, AR104: 3, L0749: 2,	AR055: 9, AR052: 7, AR060: 6, AR053: 6, AR033: 5, AR061: 5, AR096: 5, AR089: 5, AR039: 3, AR104: 3 L0666: 2, L0779: 2, S0040: 1, S0442: 1, H0634: 1, L0643: 1, L0804: 1, L0775: 1, L0809: 1, H0144:
	Arg-65 to His-70.	1894 Lys-42 to Gly-48, Asp-71 to Pro-76, Tyr-84 to Met-91.
	1893	1894
	45 - 416	48 - 506
	488	489
	851342	851343
	HE9F133	HOUBJ40
	478	479

480 HHEYCOG 851355 490 566- 1895 Pro-58 to His-69, ARO96: 9, ARO96: 7, 1723, 106- 1805 Pro-58 to His-69, ARO96: 9, ARO96: 7, 1723, 106- 1206 Glu-132 to Asn-138, ARO96: 4, ARO96: 4, ARO96: 4, ARO96: 4, ARO96: 4, ARO96: 2, ARO96: 1, HO144: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,		11/903																				CI	708	701	/104:
HESFS36 851478 491 118 - 1896 Glu-132 to Asn-138.  HESFS36 851478 491 118 - 1896 Glu-132 to Asn-138.  HEZSS47 851581 492 610 - 1897  HELD06 851722 493 243 - 1898 Tyr-25 to Val-30.	701	7-23, 106- 122, 139-	155				40-68, 1-	24, 76-92	-					-			71-108,	68-84							156-172
HESFS36 851478 491 118 - 1896 Glu-132 to Asn-138.  HESFS36 851478 491 118 - 1896 Glu-132 to Asn-138.  HEZSS47 851581 492 610 - 1897  HELD06 851722 493 243 - 1898 Tyr-25 to Val-30.		·.																	 						
HESFS36 851478 491 118 - 1896 Glu-132 to Asn-138.  HESFS36 851478 491 118 - 1896 Glu-132 to Asn-138.  HEZSS47 851581 492 610 - 1897  HELD06 851722 493 243 - 1898 Tyr-25 to Val-30.																									
HHEVC06 851355 490 566- 1895 1060 1060 1060 1060 1060 1060 1060 106	1, L0777: 1 and L0752: 1.	AR096: AR052:	AR039:	AR055: 2, AR061: 1	L0526: 1, H0144: 1,	L0748: 1 and H0543: 1.	AR039: 7, AR055: 7,	AR096: 6, AR033: 6,			L0766: 2, L0759: 2,	H0580: 1, H0611: 1, H0013:	1, S0474: 1, H0057: 1,	H0268: 1, H0413: 1, L0655:	1, L0748: 1, L0756: 1,	H0595: 1 and L0594: 1.	l .			-	S0001: 2, H0624: 1,	H0255: 1, S0428: 1, S0152:	1, S0028: 1, S0031: 1 and	S0260: 1.	AR089: 12, AR033: 12,
HHEVC06 851355 490 566- 1895 1060 1060 1060 1060 1060 1060 1060 106		Pro-58 to His-69, Glu-132 to Asn-138.																							Tyr-25 to Val-30.
HHEVC06 851355 490 HE8FS36 851478 491 HE2SS47 851581 492 HTELD06 851722 493	00,	1895					1896										1897								1898
HHEVC06 851355 HE8FS36 851478 HE2SS47 851581 HTELD06 851722		566 - 1060					118 -	456									610 -	942							243 -
HESFS36 HE2SS47 HTELD06		490					491										492								493
		851355					851478										851581								851722
481 482 483		HHEVC06					HE8FS36								•		HE2SS47								HTELD06
		480					481			-							482								483

	93-109
AR052: 11, AR060: 10, AR096: 8, AR053: 7, AR104: 5, AR039: 5, AR061: 4, AR055: 3 H0616: 2, L0665: 2, L0779: 2, H0624: 1, H0156: 1, L0766: 1, L0803: 1, L0517: 1, L0367: 1, L0792: 1, L0663: 1, L0748: 1, L0754: 1 and L0758: 1.	AR096: 5, AR052: 5, AR039: 5, AR053: 4, AR089: 3, AR033: 3, AR060: 3, AR104: 3, AR055: 2, AR061: 1 S0003: 4, L0756: 4, H0521: 3, H0171: 2, H0014: 2, S0214: 2, L0748: 2, L0747: 2, L0755: 2, H0581: 1, H0263: 1, L0471: 1, H0266: 1, H0328: 1, H0615: 1, H0553: 1, H0032: 1, H0591: 1, L0773: 1, L0766: 1, L0375: 1, L0776: 1, L0527: 1, L0759: 1, H0520: 1, H0478: 1, L0750: 1, L0779: 1, L0759: 1, S0031: 1, L0591: 1 and S0026: 1.
·	Thr-2 to Val-8, Leu-43 to Glu-48, Lys-53 to Gln-61.
	1899
098	916
	494
	851787
	нориноб
	484

FC1/0501/10450
57-79, 30- 49
AR052: 4, AR060: 2, AR033: 2, AR089: 1, AR053: 1, AR096: 1, AR055: 1, AR104: 1, AR061: 1, AR039: 0 L0748: 7, L0659: 3, L0747: 3, S0212: 2, S0010: 2, H0132: 2, L0764: 2, L0744: 2, L0752: 2, L0759: 2, S0424: 2, H0170: 1, S0116: 1, S0358: 1, S6016: 1, H0587: 1, H0575: 1, H0615: 1, H0039: 1, H0674: 1, L0471: 1, H0825: 1, H0654: 1, H0529: 1, L0364: 1, L0656: 1, L0526: 1, L0783: 1, L0532: 1, L0663: 1, L0665: 1, H0724: 1,
Lys-78 to Glu-88, Ser-93 to Glu-102, Ser-109 to Cys-117, Arg-126 to Gln-132.
1901
527
496
852568
НЕ6СН89
486

		210-237,	41-73, 84-	110, 238-	257																						79-97
														-									,				
21:								. <u>%</u>		4:		- 5:		<u>.</u> 6		<u> </u>		51:	-	<u>.</u> 9		5:		2:-			
H0658: 1, H0660: 1, H0521:	1, H0522: 1, S0406: 1 and L0740: 1.	AR089: 1, AR033: 1,	AR053: 1, AR055: 1,	AR060: 1, AR096: 1,	AR061: 0, AR039: 0,	AR104: 0, AR052: 0	H0521: 7, S0022: 6,	L0770: 6, L0769: 6, L0758:	5, S0051: 4, L0747: 4,	L0756: 4, H0638: 3, H0124:	3, L0794: 3, L0805: 3,	S0278: 2, S0222: 2, H0052:	2, H0327: 2, H0100: 2,	L0789: 2, L0438: 2, L0439:	2, L0751: 2, L0777: 2,	L0591: 2, S0282: 1, S035	1, L0717: 1, H0441: 1,	H0587: 1, L0163: 1, H0051:	1, S0048: 1, H0594: 1,	H0328: 1, L0455: 1, S0036:	1, S0038: 1, S0344: 1,	L0761: 1, L0775: 1, L0375:	1, L0776: 1, L0659: 1,	L0809: 1, L0647: 1, H0522:	1, L0750: 1, L0753: 1,	H0445: 1 and L0366: 1.	AR055: 6, AR060: 4,
		Pro-36 to Gln-42,	Cys-73 to Ser-86.	•																							Ile-37 to Phe-45,
		1902				•		-																			1903
		18 - 833																									3509 -
		497																									498
		852676																									852760
		HDPGS20																									HWBBZ12
		487																									488

WO 01/90304	PC1/US01/16450
	120-148, 100-121, 158-175
2913 Leu-109 to Glu-118, AR096: 4, AR052: 3, Ser-169 to Ser-178. AR061: 2, AR033: 1, AR089: 0, AR039: 0 L0766: 9, L0794: 6, L0749: 6, L0749: 6, L0771: 3, H0622: 2, S0422: 2, L0740: 2, L0756: 2, L0595: 2, H0402: 1, S0420: 1, S0420: 1, S0420: 1, H0280: 1, H0280: 1, H0291: 1, H0291: 1, H0291: 1, H0291: 1, L0773: 1, L0893: 1, L0773: 1, L0893: 1, L0773: 1, L0893: 1, L0773: 1, L0793: 1, L0777: 1, L0773: 1, L0	852845 499 59 - 607 1904 Lys-57 to Lys-65, AR053: 2, AR039: 2, Gln-72 to Glu-81, AR052: 1, AR060: 1, Lys-88 to Lys-93, AR089: 1, AR096: 1, Tyr-147 to Glu-156. AR061: 1, AR055: 0, AR033: 0, AR104: 0 L0731: 14, L0756: 9, H0521: 6, L0758: 6, L0759: 6, H0556: 5, L0659: 5,
	9 HDPBI36
	489

					-																							-	
-		• •						•••														**						3:	
L0783: 5, H0659: 4, S0360:	3, H0413: 3, L0598: 3,	L0770: 3, L0791: 3, L0665	3, S0126: 3, S0378: 3,	L0755: 3, H0624: 2, H0171:	2, S0358: 2, H0580: 2,	H0645: 2, T0060: 2, H0156:	2, H0042: 2, H0263: 2,	H0046: 2, S0003: 2, H0591:	2, H0616: 2, H0641: 2,	H0646: 2, S0344: 2, L0369	2, L0662: 2, L0776: 2,	L0663: 2, S0027: 2, L0779:	2, H0667: 2, S0192: 2,	H0543: 2, H0422: 2, H0170	1, H0713: 1, S0114: 1,	S0134: 1, H0583: 1, H0341:	1, S0212: 1, H0661: 1,	S0418: 1, S0444: 1, S0408:	1, S0468: 1, S0045: 1,	S0476: 1, H0639: 1, L0717:	1, H0411: 1, H0441: 1,	H0370: 1, H0331: 1, H0574:	1, H0075: 1, H0581: 1,	H0052: 1, H0123: 1, S0050.	1, H0014: 1, T0010: 1,	H0266: 1, S0250: 1, H0644:	1, L0142: 1, H0628: 1,	H0617: 1, H0032: 1, H0383:	1, H0169: 1, S0036: 1,
																					-								

	48-/4, 218-241, 91-110, 173-191, 146-162
H0551: 1, H026- 1, H0625: 1, L073: 1 1, L0803 1, L0523: 1 1, L0523: 1 1, L0666 S0374: 1 1, S0152 S0146: 1 1, S0154 S0026: 1 1, S0436 S0026: 1 1, S0436 S0026: 1 1, S0436 S0026: 1 1, S0437	1905 Glu-167 to Met-172, AR061: 9, AR089: 5, Pro-208 to Arg-218, AR060: 5, AR033: 5, Arg-243 to Ser-253, AR055: 5, AR052: 4, Ser-255 to Gly-262. AR096: 4, AR039: 3, AR053: 2, AR104: 2 S0278: 3, H0641: 3, S0142: 3, H0521: 3, H0271:
	500 167 - 952
	490 HMAEP64 852960

WO 01/90304 PCT/US01/16450

	·- ·- ·- ·		
		97-113	154-171,
and the second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second s			
2, L0770: 2, L0794: 2, L0748: 2, L0777: 2, L0599: 2, H0583: 1, H0650: 1, H0657: 1, H0656: 1, H0663: 1, H0638: 1, S0358: 1, S0376: 1, H0545: 1, S0388: 1, H0594: 1, S0144: 1, S0344: 1, L0763: 1, L0646:	1, L0648: 1, L0767: 1, L0766: 1, L0650: 1, L0775: 1, L0787: 1, L0664: 1, S0216: 1, H0576: 1, H0727: 1, L0756: 1, L0757: 1, S0260: 1 and S0436: 1.	AR033: 2, AR104: 2, AR055: 2, AR039: 2, AR060: 1, AR052: 1, AR061: 1, AR089: 1, AR053: 1, AR096: 0 L0663: 2, L0439: 2, L0731: 2, H0663: 1, H0497: 1, H0486: 1, H0124: 1, S0036: 1, H0116: 1, H0623: 1, L0633: 1, L0783: 1, L0438: 1, H0547: 1, H0670: 1, S0404: 1, L0748: 1, L0747: 1, L0485: 1, H0667:	96: 5,
2, L0770: 2, L0794: 2, L0748: 2, L0777: 2, L0 2, H0583: 1, H0650: 1, H0657: 1, H0656: 1, H 1, H0638: 1, S0358: 1, S0376: 1, H0594: 1, S0144: 1, S0344: 1, L0763: 1, L0 50344: 1, L0763: 1, L0	1, L0648: 1, L0767: 1 L0766: 1, L0650: 1, L 1, L0787: 1, L0664: 1 S0216: 1, H0576: 1, F 1, L0756: 1, L0757: 1 S0260: 1 and S0436:	AR033: 2, AR104: 2 AR055: 2, AR039: 2 AR060: 1, AR052: 1 AR061: 1, AR089: 1 AR053: 1, AR096: 0 L0663: 2, L0439: 2, L0731: 2, H0663: 1, H0 1, H0486: 1, H0116: 1, HC 1, L0633: 1, L0783: 1, L0438: 1, H0547: 1, HC 1, S0404: 1, L0748: 1, L0747: 1, L0485: 1, HC 1 and H0422: 1.	AR052: 6, AR096:
2, L0770 L0748: 2 2, H058: H0657: 1, H063 S0376: 1 1, H059 S0344: 1	1, L0648 L0766: 1 1, L0787 S0216: 1 1, L0756 S0260: 1	AR033: 2, AR104: AR055: 2, AR039: AR060: 1, AR052: AR061: 1, AR089: AR053: 1, AR096: L0663: 2, L0439: 2, L0731: 2, H0663: 1, F 1, H0486: 1, H0124: 1 S0036: 1, H0116: 1, F 1, L0633: 1, L0783: 1 L0438: 1, H0547: 1, F 1, S0404: 1, L0748: 1 L0747: 1, L0485: 1, F 1 and H0422: 1.	AR052:
		Lys-2 to Glu-21, Lys-34 to Ser-42, Ile-118 to Pro-123.	Ala-25 to Gly-32.
		1906	1907
		38 - 454	73 -
		501	502
		852980	852987
		HTYSK68	HDAAD50
		491	492

	93-121, 56-73, 36- 52
803: 7764: 747: 046: 0574: 0572: 0521:	
AR089: 5, AR033: 5, AR053: 4, AR053: 4, AR059: 3, AR060: 3, AR061: 2, AR104: 2, AR055: 2 L0439: 9, L0766: 7, H0251: 5, L0740: 5, L0803: 4, L0794: 3, L0665: 3, H0445: 3, H0156: 2, L0747: 2, L0756: 2, L0777: 2, L0756: 1, H0638: 1, H0059: 1, H0574: 1, H0559: 1, H0591: 1, H0591: 1, H0591: 1, H0590: 1, L0662: 1, L0768: 1, L0650: 1, L0775: 1, L0866: 1, L0659: 1, H0444: 1, H0702: 1, L0775: 1, L0806: 1, L0659: 1, H0445: 1, H0435: 1, H0648: 1, H0672: 1, H0435: 1, H0648: 1, H0672: 1, H0659: 1, H0667: 1, H0643: 1, L0758: 1, L0758: 1, H0643: 1, L0758: 1, H0643: 1, H0657: 1, H0423: S0260: 1, H0667: 1, H0643: S0260: 1, H0667:	1 and L0465: 1. AR096: 8, AR039: 6, AR089: 6, AR104: 5, AR060: 4, AR033: 3,
	1 and L0465: 1.  Trp-22 to Arg-30, AR096: 8, AR039: Lys-120 to Glu-127. AR089: 6, AR104: AR060: 4, AR033:
1335	28 - 408 1908
	503 28
	853174
	HNTNC03
	493

·	56-73, 225-241
R052: 3, R061: 1 358: 2, 56: 2, L0758: 0212: 1, 51: 1, T0039: 10318: 1, 15: 1, S6028: 0069: 1, 46: 1, L0646: 0662: 1, 03: 1, L0666: 0520: 1, 36: 1, L0750: 0759: 1,	2, AR096: 1, 1, AR104: 1, 1, AR052: 0, 0, AR060: 0, 0, AR055: 0 12, L0766: 11, 1, L0803: 7, S0136: 4, L0438: 3, 1, L0749: 3, H0624: 2, H0014: 2, 30422: 2, L0794:
AR053: 3, AR052: 3, AR055: 2, AR061: 1 L0748: 4, S0358: 2, L0754: 2, L0756: 2, L0758: 2, H0222: 1, S0212: 1, H0580: 1, H0351: 1, T0039: 1, H0590: 1, H0318: 1, T0071: 1, H0015: 1, S6028: 1, S0036: 1, T0069: 1, H0130: 1, H0646: 1, L0646: 1, L0773: 1, L0662: 1, L0766: 1, L0803: 1, L0666: 1, L0665: 1, H0520: 1, H0547: 1, S0136: 1, H0521: 1, H0696: 1, S0028: 1, L0743: 1, L0745: 1, L0750: 1, L0777: 1, L0759: 1, S0434: 1 and L0596: 1.	AR039: 2, AR096: 1, AR039: 1, AR104: 1, AR061: 0, AR060: 0, AR053: 0, AR055: 0 L0748: 12, L0766: 11, L0439: 8, L0803: 7, S0136: 6, L0758: 4, L0438: 3, L0751: 3, L0749: 3, H0624: 2, H0318: 2, H0014: 2, H0553: 2, S0422: 2, L0794: 2, L0663: 2, H0144: 2,
	1909
	42 - 908
	504
	853186
	HCFNG65
	494

VO 01/90304		
	138-155, 119-135	90-107
744: 0657: 412: 664: 1704:	, , , , , , , , , , , , , , , , , , ,	18, 14, 13, 10, 10, 0789:
H0555: 2, S3014: 2, L0744: 2, L0747: 2, L0485: 2, H0423: 2, H0423: 2, H0471: 1, H0657: 1, S0358: 1, H0637: 1, L0351: 1, L0475: 1, H0653: 1, L0662: 1, L0655: 1, L0659: 1, L0664: 1, L0664: 1, S0328: 1, R0521: 1, H0704: 1, L0743: 1, L0759: 1 and L0743: 1, L0759: 1 and L0768: 1	AR055: 9, AR052: 6, AR096: 6, AR060: 6, AR061: 6, AR033: 5, AR089: 4, AR053: 4, AR104: 3, AR039: 3 H0483: 1, H0255: 1, H0600: 1, H0310: 1, L0766:	21, AR033: 16, AR052: 14, AR053: 11, AR060: 10, AR061: 9, L0763: 6, H0483: 1, L
H0555: 2 2, L0747: 1, S0358: 50050: 1, 1, L0351: H0633: 1 1, L0659: L0793: 1, 1, S0328: S0350: 1, 1, L0743:	AR055: AR096: AR061: AR104: H0483: H0600: 1	
	Asp-22 to Gln-30, Lys-80 to Gly-91.	Arg-17 to Phe-28, Asp-35 to Asp-43, Gly-53 to Ala-60, Gln-127 to Trp-134, Val-156 to Lys-165.
	1910	1911
	787 - 311	87 - 590
	505	906
	853213	853966
	HLMMI85	HBGMZ39
	495	496

100-120	
29, 25, 16, 9, 5 5 10750: 1, 10090: 2, 10663: 2, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10663: 1, 10664: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 1, 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 106666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666: 10666	10620: 1,
AR039: 39, AR053: 29, AR096: 27, AR052: 25, AR033: 20, AR104: 16, AR089: 10, AR060: 9, AR055: 8, AR061: 5 L0754: 6, S0422: 5, H0547: 5, L0471: 4, L0750: 4, L0362: 4, S0360: 3, H0547: 5, L0471: 4, L0750: 2, H0548: 3, H0548: 3, S0003: 3, H0646: 3, L0740: 3, L0758: 3, H0542: 2, H0090: 2, H0556: 2, H0341: 2, H0497: 2, S6028: 2, H0663: 2, H0591: 2, H0494: 2, L0770: 2, L0655: 2, L0663: 2, S0428: 2, H0144: 2, L0777: 2, L0599: 2, L0731: 2, L0599: 2, L0608: 2, H0422: 2, H0686: 1, S0040: 1, S6024: 1, H0661: 1, H0663: 1, H0638: 1, S0420: 1, S0354: 1, S0358: 1, S0408: 1, S0476: 1, L0717: 1, H0261: 1,	H0549: 1, H0455: 1, H0586: 1, L0586: 1, H0635: 1, S0010: 1, H0569: 1, H0620: 1, H0350: 1, H0201: 1,
	H0549: 1, 1, L0586: S0010: 1, H0350:
Asp-9 to Ser-18, Ala-27 to Asn-34, Val-63 to Leu-69, Thr-91 to Thr-103, Lys-143 to Asn-148, Thr-160 to Ile-173.	
1912	
831	
202	
854202	
497 HHEIA70	
497	

·	<del></del>
	51-69, 96-
	51-69
	<u>, 11</u>
·	
.1. <del>2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2</del>	33:
H027 11, 11, 11, 11, 11, 11, 11, 11, 11, 11	3, 3, 1 1, 108(
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S0051: 1, H0179: 1, H0271: 1, S0214: 1, H0644: 1, H0628: 1, H0644: 1, H0641: 1, S0352: 1, S0440: 1, H0641: 1, S0342: 1, L0769: 1, L0520: 1, L0763: 1, L0520: 1, L0767: 1, L0772: 1, L0773: 1, L0646: 1, L0652: 1, L0667: 1, L0657: 1, L0657: 1, L0657: 1, L0659: 1, L0647: 1, L0659: 1, L0647: 1, L0659: 1, S0053: 1, H0522: 1, H0626: 1, S0152: 1, H0626: 1, L0779: 1, L0756: 1, L0779: 1, L0756: 1, L0779: 1, L0756: 1, L0779: 1, H0645:	AR039: 5, AR096: 3, AR033: 3, AR053: 3, AR060: 3, AR089: 3, AR104: 3, AR055: 2, AR052: 2, AR061: 1 H0351: 11, L0439: 5, H0090: 3, H0616: 3, L0803 3, L0777: 3, S0222: 2,
<u>» - E - E - C - C - C - C - E - E - C - C</u>	
	-88, u-119
•	Lys o Glu
	83 to
	Asn-83 to Lys-88, Ala-113 to Glu-119.
	3
	191
	538
	508
	854267
	HNTNA78
	498
	<u></u>

/ U 01/90304	PC1/US01/16450
	73-89, 26-
H0013: 2, H0318: 2, H0032: 2, L0794: 2, L0766: 2, L0806: 2, L0766: 2, L0806: 2, L0740: 2, H0170: 1, H0341: 1, S0001: 1, H0671: 1, H0663: 1, H0590: 1, H0196: 1, H0590: 1, H0590: 1, H0590: 1, H0590: 1, H0591: 1, H0591: 1, H0591: 1, H0591: 1, H0591: 1, L0660: 1, L0770: 1, L0660: 1, L0770: 1, L0660: 1, S0406: 1, S0028: 1, L0750: 1, L0758: 1, S0031: 1, S0260: 1, S0242: 1 and H0422: 1	AR039: 7, AR096: 5, AR052: 4, AR104: 4, AR033: 3, AR053: 3, AR089: 3, AR055: 3, AR060: 3, AR061: 2
	Pro-57 to Trp-62.
	1914
	288 -
	509
	854277
	HOVAN91
	499

	69-85	106-135
		300018, 300075, 300077,
		Xp22.1- p21.3
L0438: 6, L0439: 6, L0776: 5, H0428: 4, L0805: 4, H0687: 3, L0770: 3, H0651: 3, L0789: 2, L0756: 2, L0758: 2, L0361: 2, S0212: 1, S0001: 1, H0351: 1, H0052: 1, H0327: 1, H0178: 1, L0769: 1, L0767: 1, L0794: 1, L0807: 1, L0759: 1 and L0608: 1.	AR096: 4, AR052: 3, AR033: 2, AR104: 2, AR061: 2, AR053: 2, AR089: 1, AR060: 1, AR055: 1, AR039: 0 L0766: 3, L0776: 3, L0766: 2, L0748: 2, L0747: 2, L0750: 2, L0485: 2, S0001: 1, L0534: 1, S0360: 1, H0580: 1, S0051: 1, H0188: 1, H0379: 1, S0440: 1, L0761: 1, L0800: 1, L0651: 1, L0659: 1, L0517: 1, L0787: 1, H0593: 1, S0260: 1 and H0445: 1.	Leu-46 to Trp-52, Glu-90 to Arg-96, Leu-151 to Asp-159.
	22	604 1916
	510 774 - 442	511 98 - 604
	854463	854659
	HLY ER32	HFPEL47
	200	501

	245-262, 207-223
300200, 301200, 301220, 302350, 306000, 306000, 307030, 309470, 309510, 312040, 312170, 312170, 312700,	
·	58: 575:
AR053: 2, AR096: 1, AR104: 1, AR039: 1 S0222: 1	AR052: 16, AR089: 15, AR053: 13, AR039: 12, AR061: 4, AR096: 1, AR104: 1, AR055: 0 L0777: 4, H0635: 3, L0775: 3, L0731: 3, L0758: 3, S0276: 3, H0170: 2, L0470: 2, H0013: 2, H0575: 2, H0046: 2, H0622: 2, H0634: 2, L0766: 2, L0783: 2, L0809: 2, L0664: 2,
44	Pro-87 to Tyr-99, A Pro-102 to Tyr-117, A Arg-144 to Trp-150, A Phe-164 to Ile-180, A Trp-293 to Tyr-307. A J H
	1917
	551 - 1507
	512
	854779
	HTPIJ41
	502

	236-252
S0328: 2, S0152: 2, S3014: 2, L0439: 2, L0740: 2, L0747: 2, L0779: 2, L0599: 2, H0638: 1, H0411: 1, H0550: 1, H0069: 1, H0427: 1, L0021: 1, S0010: 1, L0105: 1, H0309: 1, H0674: 1, H0683: 1, S0408: 1, H0647: 1, S0406: 1, L0648: 1, L0769: 1, L0768: 1, L0769: 1, L0764: 1, L0790: 1, H0520: 1, S0126: 1, S0122: 1, H0521: 1, H0522: 1, S0044: 1, S0406: 1, H0436: 1, S3012: 1, L0754: 1, L0745: 1, L0746: 1, L0750: 1, L0769: 1, L0746: 1, L0750: 1, L0769: 1, L0769: 1, L0759: 1, L0769: 1, L0769: 1, L0759: 1, L0760: 1, S0192: 1 and S0424: 1.	8 Arg-80 to Gly-86, Gly-103 to Leu-110.
	40 - 191
	513
	855013
	HNTNC49
	L' '

									<u> </u>																		
L0743: 6, L0779: 6, L0754: 5, 1,0758: 5, 1,0761: 4.	L0771: 4, L0662: 4, L0731:	4, H0620: 3, T0006: 3,	17: 3, L0520: 3, L07/4:	L0439: 3, L0777: 3, L0595:	0657: 2, H0580: 2,	56: 2, H0618: 2, H0253:	2, H0081: 2, L0471: 2,	H0012: 2, S0366: 2, S0038:	2, H0130: 2, L0770: 2,	58: 2, L0794: 2, L0806:	0805: 2, L0657: 2,	L0666: 2, L0663: 2, H0672:	2, H0539: 2, H0696: 2,	40: 2, L0752: 2, L0759:	2, S0031: 2, L0599: 2,	H0543: 2, H0295: 1, S0116:	0341: 1, H0402: 1,	H0305: 1, H0589: 1, H0638:	1, S0418: 1, S0356: 1,	58: 1, S0360: 1, H0208:	0619: 1, H0441: 1,	H0455: 1, H0587: 1, H0333:	, L0623: 1, H0486: 1,	21: 1, H0599: 1, H0108:	1, H0042: 1, S0010: 1,	H0581: 1, H0546: 1, H0545:	1, H0046: 1, H0050: 1,
TO72	1.077	4, H	H06	105.	ј3, H(	H01.	2, Hí	00H	2, H	707	2, LC	907	2, H	L07		H05	1, H	H030	1, SC	8035	1, H	H04		1000	1, H	H05	1.H

	81-100, 13-29
1188: 1090: 100: 763: 542: 742: 689: 445:	<u></u>
H0057: 1, H0266: 1, H0188: 1, H0682: 1, H0039: 1, H0622: 1, H0424: 1, H0181: 1, H0383: 1, H0166: 1, H0673: 1, H0135: 1, H0090: 1, H0038: 1, H0135: 1, H0090: 1, H0057: 1, H0057: 1, H0057: 1, H0057: 1, H0053: 1, H0050: 1, L0648: 1, L0540: 1, L0792: 1, L0664: 1, L0438: 1, H0650: 1, H0651: 1, L0664: 1, L0438: 1, H0670: 1, H0651: 1, L0749: 1, L0756: 1, L0749: 1, L0756: 1, L0749: 1, L0756: 1, L0780: 1, H0595: 1, L0756: 1, L0780: 1, H0590: 1, H0590: 1, L0756: 1, H0659: 1, H0659: 1, H0659: 1, H0659: 1, H0659: 1, H0659: 1, L0756: 1, H0659: 1, H06608: 1, H0659: 1, H06608: 1, H0659: 1, H06608: 1, H0659: 1, H06608: 1, H0660	AR052: 18, AR053: 14, AR033: 7, AR096: 7, AR089: 6, AR060: 5, AR104: 5, AR055: 5, AR039: 3, AR061: 3
H0057: 1, 1, H0687: 1, H0622: 1, 1, H0673: 1, 1, H0038: 1, H0067: 1, 1, S0112: H0494: 1, 1, L064: 1, 1, L064: 1, 1, L0664: 1, 1, L0664: 1, 1, H0670: S0380: 1, 1, H0670: S0380: 1, 1, H0670: L0780: 1, H0595: 1, H0595: 1, H0599:	AR052: 13 AR033: 7 AR1089: 6 AR104: 5 AR039: 3
	Ser-2 to Tyr-8.
	1919
	238 - 612
	514
	855239
	HLTC094
	504

	42-62
H0059: 1, H0100: 1, S0142: 1, S0002: 1, L0369: 1, L0637: 1, L0646: 1, L0771: 1, L0649: 1, L0771: 1, L0659: 1, L0659: 1, L0659: 1, L0669: 1, L0659: 1, L0783: 1, L0544: 1, L0663: 1, S0374: 1, L0663: 1, S0374: 1, L0763: 1, H0650: 1, H0683: 1, H0660: 1, L0772: 1, L0778: 1, L0759: 1, L0778: 1, L0759: 1, L0759: 1, L0653: 1 and H0543: 1.	AR053: 4, AR033: 2, AR089: 2, AR055: 1, AR096: 1, AR104: 1, AR051: 1, AR060: 1, AR039: 0, AR052: 0 L0758: 6, L0794: 4, L0764: 3, L0809: 3, S0360: 2, H0253: 2, H0196: 2, H0052: 2, H0150: 2, H0024: 2, H0424: 2, H0606: 2, L0770: 2, L0803: 2, H0547: 2, H0593: 2, L0747: 2, L0759: 2, L0485: 2, S6024:
	Lys-8 to Gly-15, Arg-29 to Ala-34, Asp-65 to Pro-70.
	1920
	336 - 743
	515
	855274
	HBIMT77
	505

	+	
3	73-90, 152-168, 51-67, 270-286, 207-223	91-109
		, , , , , , , , , , , , , , , , , , ,
1, H0657: 1, H0341: 1, H0402: 1, S0046: 1, H0549: 1, H0608: 1, H0587: 1, H0618: 1, H0546: 1, H0123: 1, H0081: 1, H0099: 1, H0271: 1, H0328: 1, H0124: 1, H0040: 1, H0116: 1, L0475: 1, L0761: 1, L0646: 1, L0662: 1, L0363: 1, L0806: 1, L0635: 1, L0790: 1, S0330: 1, H0521: 1, L0611: 1, L0439: 1, L0751: 1 and L0749: 1.	AR039: 18, AR033: 17, AR089: 15, AR052: 14, AR055: 13, AR053: 13, AR061: 9, AR096: 9, AR060: 8, AR104: 6 H0618: 2, S0031: 2, H0545: 1, S0050: 1, H0031: 1, H0124: 1, H0130: 1, H0646: 1, H0521: 1, S0432: 1, L0601: 1 and L0600: 1.	AR033: 28, AR052: 22, AR053: 20, AR055: 20, AR089: 19, AR039: 17, AR060: 10, AR096: 10, AR061: 9, AR104: 5 L0439: 29, L0766: 11,
		1922 Met-1 to His-23, Asp-64 to Ser-79.
50	1921	1922
	94 - 1047	532 - 197
	516	517
	855314	855433
O E A A A A A A A A A A A A A A A A A A	HTLIV70	HFADF33
	206	507

	163-202, 134-159, 223-241, 113-131, 199-215, 156-172
L0742: 8, L0769: 6, L0351: 5, S0222: 4, H0052: 4, T0010: 4, S6024: 3, L0768: 3, L0779: 3, L0759: 3, H0455: 2, L0794: 2, L0776: 2, L0438: 2, S0001: 1, L0534: 1, S0049: 1, S0051: 1, S0038: 1, L0763: 1, L0770: 1, L0805: 1, L0745: 1, L0777: 1, L0753: 1 and L0758: 1.	Met-1 to Pro-7, AR061: 56, AR055: 8, Leu-55 to Tyr-60, Glu-67 to Leu-77, AR096: 6, AR052: 5, Arg-110 to Phe-115, AR104: 3, AR039: 2 H0046: 9, L0766: 8, L0731: 6, L0779: 5, L0800: 4, S0003: 3, S0408: 2, H0494: 2, S0422: 2, L0803: 2, L0804: 2, L0805: 2, L0776: 2, L0655: 2, L0748: 2, L0776: 2, L0655: 2, L0748: 1, S0222: 1, H0611: 1, L0163: 1, H0266: 1, S0214: 1, L0483: 1, L0055: 1, L0455: 1, H0038: 1, H0063: 1, H0413: 1, S0440: 1, L0770: 1, L0771: 1, L0521:
	1923 G A G L M
	538 - 1269
	518
	855453
	нетлQ73

	37-55, 60- 76, 79-95
1, L0806: 1, L0653: 1, L0659: 1, L0790: 1, L0666: 1, L0663: 1, S0126: 1, H0690: 1, H0684: 1, H0658: 1, H0710: 1, H0521: 1, H0478: 1, S0206: 1, L0740: 1, L0751: 1, L0750: 1, L0777: 1, L0758: 1, L0605: 1, L0595: 1, S0192: 1, H0543: 1, H0423: 1 and S0424: 1.	AR055: 10, AR033: 6, AR060: 5, AR089: 5, AR061: 4, AR052: 4, AR053: 4, AR096: 3, AR039: 3, AR104: 3 L0777: 14, L0769: 3, L0803: 3, L0805: 3, L0742: 3, L0439: 3, S0346: 2, L0766: 2, H0658: 2, L0749: 2, L0752: 2, L0407: 1, L0415: 1, S0116: 1, H0306: 1, H0305: 1, H0427: 1, H0441: 1, H0392: 1, H0486: 1, L0471: 1, H0687: 1, H0428: 1, H0124: 1, H0413: 1, L0471: 1, L0369: 1, L0638: 1, L0775: 1, L0651:
	1924
	- 298 - 606
	519
	855714
	HAGGV44
	509

	133-149, 17-33, 109-125	48-65
1, L0776: 1, L0518: 1, L0789: 1, L0792: 1, L0438: 1, L0352: 1, S0380: 1, S0188: 1, S0146: 1, H0576: 1, L0740: 1, L0747: 1, L0756: 1, L0779: 1, L0755: 1, L0759: 1, S0260: 1, L0601: 1, S0192: 1 and H0423: 1.	AR052: 12, AR055: 11, AR053: 10, AR089: 9, AR096: 9, AR033: 8, AR060: 8, AR061: 7, AR104: 5, AR039: 5 L0748: 4, H0441: 2, H0333: 2, H0670: 2, H0660: 2, L0439: 2, L0747: 2, L0601: 2, S0218: 1, H0650: 1, H0656: 1, H0077: 1, H0255: 1, H0013: 1, L0809: 1, L0790: 1, L0792: 1, H0689: 1, H0435: 1, H0134: 1, L0741: 1, L0759: 1 and S0042: 1.	AR104: 1, AR089: 1, AR053: 1, AR096: 1, AR060: 0, AR039: 0,
		Glu-40 to Phe-45.
	1925	1926
	38 - 778	208 - 567
	520	521
	856108	856212
	HTTDM15	HADCY76
	510	511

	52-69, 160-176	122-138	127-158, 157-185, 106-125, 49-65, 205-221
			·
33: 0, 6: 1, : 1 and	96: 2, 89: 2, 61: 1, 33: 0, 55: 0	AR060: 167, AR055: 164, AR061: 136, AR033: 116, AR039: 97, AR104: 97, AR053: 89, AR089: 83, AR052: 73, AR096: 70 S0142: 4, H0581: 1, S0250: 1 and H0521: 1.	AR033: 3, AR061: 3, AR053: 3, AR060: 2, AR089: 2, AR104: 2, AR096: 2, AR055: 1, AR039: 0, AR052: 0 S0144: 5, S0278: 3, S0142: 2, S0426: 2, L0665: 2, L0748: 2, H0556: 1, H0583: 1, H0644: 1, H0617: 1, H0606: 1, H0090: 1, S0002:
AR061: 0, AR033: 0, AR052: 0 L0749: 3, H0346: 1, H0370: 1, H0427: 1 and L0439: 1.	AR039: 3, AR096: 2, AR104: 2, AR089: 2, AR052: 1, AR061: 1, AR053: 0, AR033: 0, AR060: 0, AR055: 0 S0278: 1, H0521: 1 and 0740: 1.	AR060: 167, AR055: 164, AR061: 136, AR033: 116, AR039: 97, AR104: 97, AR053: 89, AR089: 83, AR052: 73, AR096: 70 S0142: 4, H0581: 1, S0250: 1 and H0521: 1.	3: 3, AR0 3: 3, AR0 9: 2, AR1 6: 2, AR0 9: 0, AR0 4: 5, S027 26: 2, L06 5: 2, H0556 5: 1, H0090
AR061: 0, AR052: 0 L0749: 3, H0370: 1, F L0439: 1.	AR039: AR104: AR052: AR053: AR060: S0278: L0740: 1	AR06 AR03 AR05 AR05 S014 S0250	AR03 AR08 AR09 AR03 S014 2, S04 1, H06 H0606
	Ser-4 to Ser-11.	1928 Gly-5 to Asp-11.	1929 His-11 to Tyr-17.
	1927	1928	1929
	21 - 548	525	33 - 743
	522	523	524
	856251	856301	856326
	HDPXW75	HMCDC50	514 HMADZ55
	512	513	514

	83-101	87-105	21-51, 146-164,
1, L0770: 1, L0767: 1, L0375: 1, L0659: 1, L0791: 1, H0689: 1, H0518: 1 and L0758: 1.		AR096: 1, AR033: 1, AR089: 1, AR060: 1, AR061: 0, AR052: 0, AR039: 0, AR104: 0, AR053: 0, AR055: 0 H0254: 1, H0553: 1, H0429: 1, H0538: 1 and H0520: 1.	AR039: 30, AR055: 28, AR033: 25, AR053: 19,
	1930 Met-1 to Asn-13.	Trp-9 to Gly-24, Gly-27 to Gln-34.	Gly-59 to Pro-68, Gln-87 to Lys-96,
	1930	1931	1932
	915	127 - 465	921 - 1436
	525	526	527
	856497	856506	856704
	515 HTXNB76	516 HLWDD49	HLQGX48
I			517

<del></del>	
127-143, 69-85	321-338, 581-598, 459-475, 285-301, 213-229, 177-193
	,
Gly-120 to Cys-125. AR060: 19, AR089: 16, AR052: 15, AR104: 14, AR061: 12, AR096: 12 L0766: 15, L0805: 5, H0632: 2, L0789: 2, L0740: 2, H0395: 1, H0656: 1, H0341: 1, H0574: 1, H0647: 1, S0422: 1, L076: 1, L0794: 1, L0776: 1, L0515: 1, S0216: 1, H0144: 1, H0682: 1, H0660: 1 and L0755: 1.	AR096: 7, AR033: 7, AR052: 7, AR060: 6, AR053: 5, AR089: 5, AR055: 4, AR104: 4, AR039: 3, AR061: 2 L0438: 9, L0439: 4, H0170: 3, H0615: 3, S0378: 3, L0750: 3, H0553: 2, H0090: 2, H0529: 2, L0764: 2, L0803: 2, L0804: 2, L0775: 2, L0652: 2, L0659: 2, L0809: 2, H0144: 2, S0028: 2, L0777: 2, L0779: 2, L0777: 2, L0759: 2, L0591: 2, H0624: 1, S0356: 1, S0376: 1, S0360: 1, L0717: 1, S0278: 1, H0369: 1, H0431: 1,
Gly-120 to Cys-125.	Leu-27 to Ser-35, Pro-64 to Gly-70, Glu-86 to Thr-92, Ser-100 to Glu-105, Arg-135 to Arg-140, Thr-366 to Cys-378, Asp-395 to His-400, Glu-436 to Arg-442, Glu-478 to Asn-486, Ser-530 to Asp-538, Glu-614 to Gly-625, Ile-637 to Leu-643.
	1933
	335 - 2263
	528
	856745
	H2CBH17
	518

	99-121
H0586: 1, H0574: 1, H0013: 1, H0427: 1, H0122: 1, H0052: 1, T0110: 1, L0118: 1, H0050: 1, H0054: 1, H0054: 1, H00594: 1, S0003: 1, H00591: 1, H00594: 1, S0003: 1, H0591: 1, H0594: 1, H0551: 1, H0591: 1, H0551: 1, H0561: 1, H0561: 1, H0561: 1, L0772: 1, L0800: 1, L0773: 1, L0772: 1, L0657: 1, L0665: 1, H0684: 1, H0660: 1, H0672: 1, H0548: 1, S0136: 1, H0543: 1, L0752: 1, H0548: 1, L0756: 1, H0543: 1, L0752: 1, H0548: 1, L0756: 1, H0543: 1, L0752: 1, L0557: 1, H0543: 1, L05	529 70 - 432 1934 Pro-17 to Gly-31. AR055: 6, AR061: 6, AR060: 3, AR053: 3, AR096: 3, AR033: 3, AR089: 2, AR052: 2, AR089: 2, AR104: 1 L0604: 8, L0485: 6, L0748: 5, L0777: 3, S0438: 2, L0809: 2, H0722: 1, H0574: 1, H0041: 1, H0708: 1, S0366: 1, L0747: 1,
	HLQEF25 856748 5
	519 HLG

	41-57,	34-51
	·	
L0749: 1, L0780: 1 and L0759: 1.	AR096: 3, AR089: 3, AR055: 3, AR060: 2, AR052: 1, AR061: 1, AR104: 1, AR039: 0 H0585: 8, H0265: 3, H0141: 2, S0360: 2, H0251: 2, H0031: 2, H0551: 2, H0529: 2, L0519: 2, L0545: 2, L0664: 2, H0668: 2, S0040: 1, T0049: 1, H0656: 1, H0255: 1, S0376: 1, S0132: 1, H0546: 1, H0375: 1, S0314: 1, H0428: 1, H0039: 1, L0643: 1, L0055: 1, L0651: 1, L0651: 1, L0776: 1, L0659: 1, L0790: 1, L066: 1, H0519: 1, S0126: 1, H0521: 1, H0576: 1, L0777: 1, L0757: 1, L0759: 1, L0777: 1, L0757: 1, L0759: 1, H0665: 1, S0194: 1 and S0458: 1.	AR055: 12, AR061: 7, AR052: 7, AR060: 7,
	1935	1936
	12 - 881	299 - 613
		531
	856923	856982
	нтона37	HLHAW26
	520	521

	79-104, 109-127, 47-63	127-150, 160-176	134-152
AR089: 6, AR033: 5, AR096: 5, AR053: 5, AR039: 3, AR104: 3 H0144: 3, H0208: 1, H0369: 1 and H0024: 1.	AR039: 23, AR053: 14, AR096: 11, AR033: 11, AR104: 10, AR052: 9, AR089: 9, AR055: 7, AR060: 7, AR061: 4 H0494: 1	AR039: 32, AR053: 22, AR033: 19, AR052: 18, AR089: 17, AR055: 17, AR104: 13, AR096: 13, AR060: 12, AR061: 10 H0295: 1 and S0330: 1.	AR055: 7, AR052: 6, AR053: 5, AR033: 4, AR061: 4, AR096: 4, AR060: 4, AR089: 4, AR039: 3, AR104: 1 L0439: 4, L0748: 3, L0731: 3, H0265: 2, H0015: 2, H0083: 2, H0040: 2, L0764: 2, L0766: 2, L0543: 2, S0027: 2, L0758: 2, L0759: 2, L0604: 2, H0685: 1, H0656: 1, S0360: 1,
	Asn-26 to Asn-31, Ser-67 to Ala-74, Ile-105 to Lys-110.	Ala-5 to Lys-36, Ser-41 to Leu-80, Gly-98 to Gly-112, Gly-198 to Asp-203.	Gln-56 to Pro-65, Pro-70 to Asn-76, Gly-85 to Trp-94, Arg-103 to Ser-108.
	1937	1938	1939
	281 - 679	45 - 653	263 - 793
	532	533	534
	857100	857311	857404
	HKAAZ46	HAQAF12	HTXEX35
	522	523	524

	130-162, 171-187	70-87, 119-135
·		
S0045: 1, L0717: 1, S0222: 1, H0156: 1, H0575: 1, H0046: 1, H0014: 1, H0266: 1, H0674: 1, H0529: 1, L0769: 1, L0645: 1, L0363: 1, L0768: 1, L0768: 1, L0776: 1, L0779: 1, L0665: 1, L0438: 1, H0682: 1, H0648: 1, L0779: 1, L0752: 1, H0444: 1, L0608: 1, H0668: 1 and H0423: 1.	AR061: 4, AR033: 3, AR055: 3, AR053: 3, AR060: 2, AR104: 2, AR089: 2, AR039: 1, AR052: 1, AR096: 1 H0013: 1 and S0250: 1.	AR055: 13, AR033: 11, AR053: 10, AR052: 9, AR089: 8, AR060: 8, AR104: 6, AR096: 4, AR104: 4, AR039: 3 S0418: 2, H0046: 2, H0542: 2, H0341: 1, H0421: 1, H0052: 1, L0471: 1, S0022: 1, H0038: 1, H0433: 1, H0560: 1, H0132: 1, S0374: 1, S3014: 1, L0759:
S0045: 1, 1, H0156: H0046: 1, 1, H0687: H0674: 1, 1, L0645: L0768: 1, 1, L076: L0665: 1, 1, H0648: L0752: 1, 1, H0668:	AR061: AR055: AR060: AR089: AR052: H0013: 1	AR055: 13, AR033 AR053: 10, AR052 AR089: 8, AR060: AR061: 6, AR096: AR104: 4, AR039: S0418: 2, H0046: 2 H0542: 2, H0341: 1 1, H0052: 1, L0471: S0022: 1, H0038: 1, 1 H0560: 1, H0132 S0374: 1, S3014: 1,
	Gln-14 to Ala-21, Leu-45 to Arg-51, Arg-54 to Asp-61, Ser-88 to Ile-95, Leu-111 to Gln-117.	
	1940	1941
	151 - 831	87 - 872
	535	536
·	857478	857623
	HE8TE64	HL3AC38
	525	526

	204-225, 142-158,	82-98, 6-	22															-										
1 and S0276: 1.				AR061: 5, AR104: 5	H0494: 12, L0770: 12,	H0657: 11, H0659: 9,	L0774: 8, L0776: 8, H0648:	8, L0755: 8, S0410: 6,	L0769: 6, L0766: 6, L0750:	6, H0638: 5, S0408: 5,	H0559: 5, S0440: 5, L0775:	5, H0520: 5, H0556: 4,	H0341: 4, S0418: 4, S0358:	4, S0376: 4, S0360: 4,	H0617: 4, L0665: 4, L0748:	4, L0777: 4, L0752: 4,	L0759: 4, S0434: 4, S0420:	3, H0253: 3, H0424: 3,	H0616: 3, H0560: 3, L0374:	3, H0144: 3, L0439: 3,	L0740: 3, L0747: 3, L0731:	3, L0758: 3, L0596: 3,	L0601: 3, S0026: 3, S0194:	3, H0170: 2, H0265: 2,	H0685: 2, H0656: 2, L0415:	2, S0444: 2, S0278: 2,	H0550: 2, H0257: 2, T0109:	2, H0156: 2, H0618: 2,
	Gln-68 to Gln-74.																											
	1942															•												
	11 - 955																				-							
	537				•							,																
	857664																	· · · · · · · · · · · · · · · · · · ·										
	HMUA031																											
	527																											

	110-135, 69-85, 47- 63
H0014: 1, H0510: 1, H0375: 1, H0188: 1, S0022: 1, H0428: 1, H0708: 1, S0366: 1, H0135: 1, H0634: 1, H0063: 1, H0063: 1, H0063: 1, H0067: 1, H0413: 1, H0646: 1, H0100: 1, T0042: 1, L0475: 1, H0386: 1, H0646: 1, L0598: 1, H0529: 1, L0373: 1, L0773: 1, L0520: 1, L0520: 1, L0520: 1, L0521: 1, L0542: 1, L0526: 1, L0540: 1, L0542: 1, L0540: 1, H0691: 1, H0691: 1, H0691: 1, H0691: 1, H0651: 1, S0330: 1, H0539: 1, S0378: 1, L0749: 1, L0749: 1, L0749: 1, L0749: 1, L0749: 1, L0749: 1, L0757: 1, L0668: 1, H0653: 1, H0669: 1, H0668: 1, H0653: 1, H0667: 1, R0668: 1, H0653: 1, H0667: 1, S0276: 1 and H0422: 1.	AR033: 4, AR052: 3, AR039: 3, AR053: 3, AR104: 3, AR089: 3,
	Met-1 to Ser-9, Ser-11 to Val-21, Gln-64 to Pro-69,
	1943
	407 - 1132
	538
	857697
	HHAWD3 3
	528

	43-59	128-144, 346-362,
	·	
Arobe: 3, Arobe: 2, Asp-106 to Gly-116. AR055: 2, Arobel: 2 L0757: 3, S0410: 2, H0052: 2, L0794: 2, L0766: 2, L0806: 2, L0809: 2, L0750: 2, L0593: 2, S0418: 1, L0534: 1, S0442: 1, S0408: 1, H0619: 1, H0036: 1, H0318: 1, H00619: 1, H0267: 1, L0455: 1, H0619: 1, H0412: 1, L0455: 1, L0768: 1, L0803: 1, L0763: 1, L0768: 1, L0803: 1, L0804: 1, L0776: 1, L0542: 1, L0789: 1, H0547: 1, S0152: 1, L0740: 1, L0754: 1, L0599: 1, L0594: 1, S0196: 1, H0423: 1 and H0506: 1.	AR060: 2, AR089: 2, AR053: 1, AR061: 1, AR033: 1, AR096: 0, AR104: 0, AR055: 0, AR039: 0 S0001: 1, H0333: 1 and S3020: 1.	AR055: 11, AR052: 10, AR096: 8, AR060: 8,
Thr-88 to Arg-96, Asp-106 to Gly-11.	Tyr-29 to Thr-34, Pro-87 to Lys-97.	
	1944 1944	1945
	90 - 404	80 - 1324
	539	540
	857723	857743
	HTZMB08	HJBCE86
	529	530

307-323	27-51, 126-147
AR104: 8, AR039: 7, AR053: 7, AR089: 7, AR033: 7, AR061: 5 L0748: 4, H0333: 2, L0766: 2, H0556: 1, S0114: 1, S0116: 1, S0360: 1, H0438: 1, H0156: 1, H0599: 1, H0706: 1, H0590: 1, H0135: 1, H0264: 1, T0042: 1, L0783: 1, L0809: 1, L0544: 1, L0666: 1, L0663: 1, S0052: 1, L0439: 1, L0749: 1, S0434: 1, L0595: 1 and S0424: 1.	AR096: 13, AR052: 11, AR053: 10, AR033: 10, AR089: 9, AR055: 9, AR104: 8, AR060: 8, AR104: 8, AR039: 5 L0809: 7, H0658: 6, L0748: 6, S0222: 5, L0794: 5, L0776: 5, L0756: 5, L0752: 5, L0731: 5, L0770: 4, L0662: 4, L0743: 4, L0439: 4, L0751: 4, L0754: 4, L0747: 4, L0759: 4, H0013: 3, L0769: 3, L0805: 3, L0789: 3, L0664: 3, L0740: 3, L0777: 3, L0753: 3, L0758: 3, H0333: 2,
	6 Pro-2 to His-10, Pro-13 to Gly-19, Ser-23 to Arg-29.
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		111-129
H0052: 2, H0545: 2, H0428: 2, L0483: 2, L0455: 2, H0509: 2, L0763: 2, L0771: 2, L0806: 2, L0804: 2, L0806: 2, L0527: 2, L0748: 2, L0666: 2, L0527: 2, L0744: 2, L0745: 2, L0745: 2, L0746: 1, H0686: 1, S0116: 1, H0255: 1, H0686: 1, S0418: 1, S0418: 1, S0418: 1, H0393: 1, L0717: 1, H0351: 1, H0156: 1, H0699: 1, H0509: 1, H0178: 1, H0178: 1, H0033: 1, H0178: 1, L0641: 1, L0768: 1, L0641: 1, L0768: 1, L0657: 1, L0636: 1, L0657: 1, L0665: 1, H0660: 1, S0027: H0660: 1, S00432: 1, S004441414141414141414141414141414141414	0/50: 1, S0011: 1.	R055: 6,
H0052: 2, H0545: 2, H0428: 2, L0483: 2, L0483: 2, L0485: 2, H0509: 2, L0763: 2, L0771: 2, L0806: 2, L0763: 2, L0771: 2, L0806: 2, L0804: 2, L0806: 2, L0663: 2, L0663: 2, L0748: 2, L0748: 2, L0748: 2, L0748: 2, L0748: 1, H0686: 1, S0146: 2, L0747: 1, H0645: 1, H0393: 1, L0717: 1, H0590: 1, H0178: 1, H0071: 1, H0178: 1, H0071: 1, L0748: 1, L0748: 1, L0778: 1, L0641: 1, L0768: 1, L0748: 1, L0665: 1, H0650: 1, H0650: 1, H0650: 1, H0660: 1, R0660: 1, H0660: 1, R0620: 1, S0027: H0660: 1, H0660: 1, S0027: H0660: 1, H0660: 1, H0660: 1, R060: 1, H0660: 1, H0660: 1, R060: 1, H0660: 1, R060: 1, H0660: 1, R060: 1, R	1, LU/42: 1, LU/50: 1, L0757: 1 and S0011: 1	AR033: 7, AR055:
		Lys-99 to Tyr-110,
		Lys-99
		1947
		224 -
		542
		857844
		HAPSP72
		532

WO 01/90304

	47-66
AR052: 6, AR060: 5, AR096: 5, AR053: 5, AR089: 4, AR104: 3, AR061: 3, AR039: 2 L0777: 5, L0766: 3, L0740: 3, L0665: 2, H0521: 2, L0748: 2, L0779: 2, L0752: 2, H0624: 1, S0420: 1, S0442: 1, L0428: 1, H0619: 1, H0431: 1, H0575: 1, H0318: 1, L0719: 1, S0214: 1, H0598: 1, H0591: 1, H0616: 1, S0422: 1, L0770: 1, L0742: 1, L0770: 1, L0742: 1, L0743: 1, L0744: 1, L0751: 1, L0747: 1, L0756: 1, L0759: 1 and S0242: 1.	AR033: 13, AR096: 9, AR052: 9, AR060: 8, AR089: 8, AR053: 8, AR055: 8, AR061: 5, AR039: 4, AR104: 4 L0770: 10, L0754: 8, L0731: 8, S0358: 6, S0414: 6, H0255: 5, S0022: 4, H0627: 4, L0757: 4, H0657: 3, H0090: 3, H0539: 3, L0755: 3, L0759: 3, S0026: 3, H0556: 2, S0007: 2,
Pro-145 to Leu-152, Pro-177 to Thr-182.	1948 Pro-23 to Glu-29, Tyr-39 to Ser-46, Pro-69 to Asp-89, Asp-112 to Pro-117.
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H0438: 2, S0214: 2, H0135:	L0803: 2, L0804: 2, L0806: L0803: 2, L0804: 2, L0806: 2, L0789: 2, L0663: 2,	\$0330: 2, L0740: 2, L0747:	L0596: 2, L0591: 2, S0040:	1, H0656: 1, S0001: 1, H0254: 1, S0418: 1, S0356:	1, H0229: 1, S0046: 1,	H0619: 1, H0645: 1, H0550:	1, H0392: 1, H0331: 1,	Т0039: 1, Н0635: 1, Н0427:	1, S0280: 1, H0036: 1,	S0010: 1, S0049: 1, H0546:	1, H0457: 1, L0471: 1,	H0620: 1, H0051: 1, S0051:	1, T0010: 1, H0179: 1,	S0250: 1, H0252: 1, L0143:	1, L0455: 1, S0036: 1,	H0040: 1, H0616: 1, H0551:	1, H0412: 1, H0059: 1,	H0494: 1, S0144: 1, S0142:	1, S0002: 1, L0521: 1,	L0662: 1, L0774: 1, L0775:	1, L0809: 1, L0647: 1,	H0144: 1, S0374: 1, L0438:	1, H0520: 1, H0593: 1,	H0683: 1, H0684: 1, H0660:	1, H0672: 1, H0522: 1,
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	26-58, 49- 65	77-95,
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S0037: 1, S0028: 1, L0748: 1, L0756: 1, L0777: 1, H0343: 1, L0605: 1, L0485: 1, L0599: 1, L0593: 1, L0366: 1, S0011: 1, H0665: 1 and H0543: 1.	AR055: 8, AR060: 4, AR052: 4, AR061: 4, AR033: 3, AR053: 3, AR089: 3, AR096: 2, AR104: 2, AR039: 1 H0616: 3, H0619: 1, H0457: 1, H0090: 1, H0038: 1, S0422: 1, L0804: 1 and L0754: 1.	AR055: 7, AR060: 6, AR052: 5, AR089: 5, AR033: 5, AR104: 4, AR039: 4, AR053: 4, AR096: 3, AR061: 3 H0124: 13, L0809: 7, L0601: 4, S0358: 2, L0666: 2, H0670: 2, L0439: 2, H0556: 1, S0420: 1, S0442: 1, H0619: 1, H0614: 1, H0587: 1, H0581: 1, H0457: 1, H0078: 1, H0271: 1, H0031: 1, H0617: 1, H0135: 1, L0762: 1, L0769: 1,
	Leu-10 to Tyr-20, Leu-24 to Ser-30.	1950 Cys-26 to Ser-32, Pro-66 to Arg-77.
	1949	1950
	24 - 347	72 - 422
	445	545
	857964	857977
	HLTE024	HHFJP51
	534	535

	172-190,
L0373: 1, L0800: 1, L0662: 1, L0363: 1, L0794: 1, L0803: 1, L0774: 1, L0775: 1, L0375: 1, L0665: 1, L0664: 1, L0665: 1, L0664: 1, L0665: 1, L0682: 1, H0658: 1, S0152: 1, L0779: 1, L0596: 1 and L0592: 1.	AR033: 19, AR039: 14, AR089: 10, AR055: 9, AR053: 9, AR052: 8, AR096: 6, AR060: 6, AR061: 6, AR104: 4 L0745: 13, L0769: 7, S0036: 6, L0753: 5, S0031: 5, H0052: 4, H0327: 4, H0046: 4, H0051: 4, T0006: 4, L0742: 4, L0746: 4, L0756: 4, L0752: 4, S6024: 3, S0282: 3, H0619: 3, S0388: 3, S0051: 3, L0741: 3, L0749: 3, S0222: 2, S0049: 2, S6028: 2, L0806: 2, L0776: 2, L0438: 2, L0777: 2, S0035: 1, H0662: 1, H0438: 1, L0021: 1, H0575: 1, S0182: 1, H0310: 1, H0009: 1, H0050: 1,
,	Arg-17 to Trp-23, Asp-37 to Asp-45, Gln-66 to Gly-75, Ser-137 to Ala-144.
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	162 - 842
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	858001
	HHFLL87
	536

WO 01/90304 PCT/US01/16450

VU 01/90304		PC 1/US01/10
	89-105, 1- 17	81-97
1, H0604: 1, L0456: 1, L0763: 1, L0770: 1, L0630: 1, L0381: 1, L0774: 1, L0775: 1, L0805: 1, L0659: 1, L0788: 1, H0689: 1, H0684: 1, H0670: 1, H0134: 1, H0478: 1, L0612: 1, L0743: 1, L0747: 1, L0779: 1, L0758: 1, S0260: 1 and L0366: 1.	AR096: 2, AR033: 2, AR055: 2, AR053: 1, AR104: 1, AR089: 1, AR061: 1, AR060: 1, AR039: 0, AR052: 0 H0553: 2, T0049: 1, H0656: 1, H0402: 1, H0125: 1, S0045: 1, H0619: 1, H0586: 1, T0114: 1, H0581: 1, H0628: 1, H0551: 1, S0310: 1, H0520: 1, H0539: 1, H0521: 1, L0779: 1, S0434: 1 and L0485: 1.	AR039: 2, AR055: 1, AR061: 1, AR104: 1, AR060: 0, AR089: 0, AR033: 0, AR096: 0, AR052: 0, AR053: 0 L0749: 3, H0341: 1 and
·	Leu-69 to Asp-76.	Pro-30 to His-50.
	1952	1953
	33 - 542	75 - 431
	547	548
	858010	858020
	HCUDR30	HHFHI24
	537	538

	94-113, 17-33	7-31, 56- 73, 39-55	95-130, 120-136
H0050: 1.	AR104: 513, AR061: 376, AR055: 327, AR060: 253, AR033: 188, AR089: 172, AR039: 115, AR053: 110, AR052: 101, AR096: 87 H0036: 1, H0050: 1 and H0673: 1.	AR055: 7, AR089: 6, AR033: 5, AR096: 5, AR104: 4, AR060: 4, AR061: 4, AR039: 3, AR052: 3, AR053: 3 L0748: 2, L0749: 2, H0085: 1, H0050: 1, H0090: 1 and L0758: 1.	AR039: 8, AR089: 2, AR052: 2, AR061: 1, AR060: 1, AR096: 0, AR033: 0, AR104: 0 L0758: 9, L0748: 6, L0747: 6, L0779: 5, L0750: 4, H0556: 3, L0804: 3, H0658: 3, H0656: 2, L0770: 2, L0769: 2, L0774: 2, H0144: 2, H0648: 2, L0439: 2, L0749: 2, L0596: 2, H0265: 1, S0444: 1, H0318: 1, H0597: 1, H0050: 1,
	·		Thr-30 to Ala-35, Ala-72 to Trp-83, Thr-138 to Ala-151.
	1954	1955	1956
	163 - 573	517 - 945	
	549	550	551
	858030	858073	858104
	HSIA148	HHFBP47	HKADE35
	539	540	541

											67-88, 3-	30, 34-52,	96-123																
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H0024: 1, H0135: 1, H0090:	1, H0038: 1, H0616: 1,	H0494: 1, L0065: 1, S0422:	1, H0529: 1, L0637: 1,	L0764: 1, L0768: 1, L0794:	1, L0387: 1, L0803: 1,	L0788: 1, L0790: 1, L0664:	1, L0438: 1, H0555: 1,	L0780: 1, L0731: 1, H0444:	1, H0542: 1, H0543: 1 and	H0423: 1.	AR033: 3, AR089: 2,	AR053: 2, AR055: 2,		AR061: 1, AR096: 1,	AR039: 1, AR052: 0	L0731: 9, L0803: 8,	H0436: 6, L0740: 6, L0756:	6, L0805: 5, L0754: 5,	L0783: 4, L0747: 4, L0749:	4, L0777: 4, H0556: 3,	H0013: 3, L0771: 3, L0794:	3, L0774: 3, L0775: 3,	L0809: 3, L0665: 3, L0757:	3, L0759: 3, L0599: 3,	H0422: 3, H0341: 2, L0005:	2, S0046: 2, H0586: 2,	H0427: 2, S0280: 2, H0201:	2, H0553: 2, H0040: 2,	H0551: 2, T0042: 2, L0770:
											Ser-122 to Trp-131.			. 7	7							· · ·		<u> </u>				Cy.	
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), LC 073 043 043 058 058	., SQ 022 H, H, E	H, Q, H, 22 H	102 H, 102 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 100 N, 10	3,5,2,5,E	9
9,5,8,5,6,5,6,7,6,7,6,7,6,7,6,7,6,7,6,7,6,7,6	1, S: 1, S: 1, S: 1, S: 1, H; 1, H; H; H; H; H; H; H; H; H; H; H; H; H;	7: 1 1, L 5: 1 0. 5	, <del>, , , , , , , , , , , , , , , , , , </del>		1, S
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	76-99,	314-332,	337-357,	383-400,	106-124,	141-157,	271-287,	242-258,	297-313					*														
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1, S0026: 1, H0136: 1, H0216: 1 and H0506: 1.	1.	AR089: 1, AR104: 1,		AR053: 0, AR039: 0,	AR052: 0, AR055: 0	L0752: 13, S0003: 11,	.0754: 11, L0794: 9,	H0521: 7, L0777: 6, H0250:	5, L0770: 5, L0766: 5,	.0755: 5, S0242: 5, H0543:	5, H0046: 4, L0803: 4,	.0804: 4, S0196: 4, H0556:	, S0440: 3, H0529: 3,	.0756: 3, L0599: 3, H0220:	2, H0638: 2, S0408: 2,	H0486: 2, H0581: 2, S0214:	2, H0553: 2, H0652: 2,	S0422: 2, L0771: 2, L0773:	2, L0775: 2, L0806: 2,	L0805: 2, L0779: 2, H0542:	2, L0600: 2, H0656: 1,	0358: 1, S0360: 1, S0476:	1, H0393: 1, H0270: 1,	.0021: 1, H0318: 1, H0421:	, H0596: 1, H0572: 1,	H0057: 1, H0373: 1, H0355:	1, H0375: 1, H0674: 1,	H0090: 1, H0634: 1, H0646:
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	102-118
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1, L0769: 1, L0372: 1, L0764: 1, L0387: 1, L0784: 1, L0607: 1, L0659: 1, L0788: 1, L0666: 1, L0663: 1, S0148: 1, H0659: 1, H0651: 1, S0328: 1, H0539: 1, S0152: 1, H0478: 1, L0748: 1, L0740: 1, L0731: 1, L0759: 1, L0362: 1, H0422: 1 and S0424: 1.	AR033: 2, AR060: 2, AR089: 1, AR061: 1, AR096: 1, AR039: 0, AR104: 0, AR052: 0, AR104: 0, AR053: 0 L0439: 5, H0592: 2, H0039: 2, H0494: 2, L0662: 2, L0659: 2, H0521: 2, L0748: 2, S0218: 1, H0657: 1, S0418: 1, S0376: 1, H0581: 1, H0596: 1, H0050: 1, H0014: 1, H0622: 1, H0038: 1, L0564: 1, H0561: 1, S0422: 1, L0770: 1, L0800: 1, L0768: 1, L0803: 1, L0805: 1, L0776: 1, L0518: 1, L0759: 1, H0520: 1, L0779: 1, L0759: 1,
	Asn-5 to Glu-15.
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WU 01/90304					FC1/C	301/10450
73-98, 8- 26, 100-	2					
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L0592: 1, L0593: 1, H0543: 1 and H0506: 1. AR053: 10, AR052: 10, AR089: 8, AR096: 7,	AR053: 4, AR050: 3, AR061: 3, AR055: 2, AR104: 2, AR039: 0 S0410: 11, L0803: 4, L0659: 4, H0618: 3, H0135:	3, L0637; 3, L0609; 3, L0666; 3, H0696; 3, L0779; 3, S0376; 2, S0132; 2, H0592; 2, H0253; 2, H0050; 2, H0087; 2, H0560; 2,	L0761: 2, S0374: 2, L0743: 2, L0751: 2, L0749: 2, L0731: 2, L0759: 2, H0542: 2, H0543: 2, H0171: 1,	H0225: 1, H0341: 1, S0212: 1, H0483: 1, S0444: 1, S0408: 1, H0393: 1, L0717: 1, H0370: 1, H0249: 1, H0360:	1, H0706: 1, T0048: 1, H0581: 1, H0545: 1, H0009: 1, H0024: 1, H0271: 1, H0288: 1, H0617: 1, S0364:	1, H0163: 1, H0551: 1, H0488: 1, H0100: 1, H0494: 1, L4497: 1, L0770: 1,
Arg-44 to Gln-55.						
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22 - 417						
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HHESR56						,

	28-61, 91- 109, 9-25, 71-87	266-295, 243-266, 302-318, 82-98
L0769: 1, L5575: 1, L5565: 1, L3905: 1, L0646: 1, L0764: 1, L0766: 1, L0650: 1, L0774: 1, L0790: 1, L0664: 1, L0665: 1, S0126: 1, H0711: 1, S0330: 1, H0436: 1, S0392: 1, S0037: 1, L0742: 1, L0755: 1, L0758: 1, H0445: 1, H0653: 1 and H0423: 1.	AR096: 2, AR055: 1, AR089: 1, AR061: 0, AR060: 0, AR104: 0, AR039: 0 L0766: 2, L0749: 2, H0650: 1, H0581: 1, H0252: 1, H0538: 1, L0771: 1, L0809: 1, L0747: 1, L0757: 1 and H0543: 1.	AR039: 2, AR104: 1, AR096: 1, AR061: 1, AR089: 1, AR060: 1, AR053: 0, AR033: 0, AR055: 0, AR052: 0 L0761: 8, L0806: 5, H0593: 5, H0436: 5, H0581: 4, H0052: 4, L0766: 4, H0521: 4, L0745: 4, L0731:
	Leu-115 to Pro-129.	1962 Met-1 to Glu-8, Glu-37 to Asp-58, Gln-75 to Leu-81.
	1961	1962
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	673-697, 319-335, 635-651, 804-820, 438-454, 876-892
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	Met-1 to Ser-6, Leu-10 to Ser-17, Met-20 to Ser-25.
	1963
	47 - 3001
	258
	HCEVS49
	548

	59-77, 87- 103, 142-
8: 1, S0358: 2261: 1, 50: 1, T0039: 3474: 1, 10: 1, H0046: 3057: 1, 42: 1, H0494: 6002: 1, 72: 1, L0800: 3363: 1, 49: 1, L0783: 3375: 1, 56: 1, S0148: 56: 1, S0148: 56: 1, S0148: 56: 1, S0148: 56: 1, S0148: 56: 1, S0148: 56: 1, S0148: 56: 1, S0148: 56: 1, S0148: 56: 1, S0148: 56: 1, S0148: 56: 1, S0148: 56: 1, S0148: 56: 1, H0436: 5777: 1, 51: 1, H0665: 55: 1, H0665: 55: 1, H0665:	to53: 1, to33: 1,
S0040: 1, S0418: 1, S0358: 1, S0376: 1, H0261: 1, H0549: 1, H0550: 1, T0039: 1, H0194: 1, S0474: 1, H0194: 1, T0110: 1, H0046: 1, H0012: 1, S0051: 1, H0266: 1, H0181: 1, L0456: 1, H0040: 1, H0040: 1, H0087: 1, H0529: 1, L0772: 1, L0800: 1, L0662: 1, L0772: 1, L0803: 1, L0794: 1, L0649: 1, L0803: 1, L0794: 1, L0658: 1, L0793: 1, L0774: 1, L0774: 1, L0779: 1, L0790: 1, L0666: 1, S0148: 1, L0792: 1, L0666: 1, S0148: 1, L0792: 1, H0670: 1, H0665: 1, H0667: 1, H0608: 1 and H0367: 1	
	- 1964 Leu-21 to Tyr-28.
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158, 186-202	59-75, 232-248, 177-193	106-123, 23-39
AR061: 1, AR060: 0, AR052: 0, AR055: 0, AR104: 0 H0266: 2, L0748: 2, L0777: 2, H0486: 1, H0373: 1, H0494: 1, S0014: 1, H0538: 1, L0803: 1, S0044: 1, L0740: 1, L0779: 1, L0759: 1, H0445: 1 and H0665: 1.	His-87 to Glu-93, AR096: 20, AR089: 16, Pro-217 to Leu-222, AR052: 13, AR053: 10, Glu-224 to Lys-230, AR039: 9, AR104: 9, Val-264 to Trp-275, AR060: 8, AR055: 8, Phe-311 to Asn-316, AR033: 6, AR061: 4 Asp-344 to Gly-349, S0476: 2, H0713: 1, Gly-363 to Gln-379, H0580: 1, S0045: 1, S0132: Gly-398 to Gly-404, 1, H0599: 1, L0143: 1, Gly-437 to Ser-446. H0551: 1, H0488: 1, S0126: 1, L0777: 1, L0731: 1, L0485: 1 and S0242: 1.	AR096: 17, AR039: 14, AR089: 12, AR060: 11, AR055: 11, AR053: 10, AR033: 10, AR104: 9, AR052: 9, AR061: 5 H0556: 1, S0420: 1, S0358: 1, H0619: 1, H0373: 1, H0702: 1, S0027: 1,
	His-87 to Glu-93, Pro-217 to Leu-222, Glu-224 to Lys-230, Val-264 to Trp-275, Phe-311 to Asn-316, Asp-344 to Gly-349, Gly-363 to Gln-379, Gly-398 to Gly-404, Gly-398 to Ser-446.	Ile-49 to Gln-55, Phe-57 to Ala-63.
	1965	1966
	105 - 1442	989 - 69
		561
	858436	858449
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	550	551

	107-129, 62-78, 81- 97	47-63
H0423: 1 and H0422: 1.	AR055: 6, AR052: 4, AR033: 4, AR053: 4, AR060: 3, AR061: 3, AR066: 2, AR089: 2, AR039: 2, AR039: 2, AR039: 2, AR039: 2, AR039: 6, H0012: 3, H0266: 3, L0770: 3, L076: 13, L0655: 3, L0776: 2, L0776: 2, L0776: 2, L0776: 2, L0776: 2, L0776: 1, S0024: 1, H0656: 1, H0656: 1, H0671: 1, H0638: 1, H033: 1, H0412: 1, L0775: 1, L0665: 1, H0672: 1, L0769: 1, L0665: 1, H0672: 1, L0743: 1, L0750: 1, L0743: 1, L0750: 1, L0750: 1, L0743: 1, L0750: 1, L0750: 1, H0423: 1, S0456: 1 and H0506: 1.	AR033: 2, AR060: 2, AR053: 2, AR096: 2, AR039: 2, AR104: 1,
	Glu-46 to Arg-53.	Pro-8 to Leu-14.
	1967	1968
	966	213 - 749
	262	563
	858450	858451
	HOUED48	HHBB126
	552	553

	79-98, 39- 56, 15-31	10-43, 111-132, 78-96, 39- 55
AR089: 1, AR055: 1, AR061: 1, AR052: 0 H0583: 1, H0650: 1, H0250: 1, H0599: 1, H0373: 1, H0266: 1, S0038: 1, S0044: 1, S0028: 1 and H0653: 1.	AR052: 2, AR053: 2, AR055: 2, AR096: 2, AR061: 1, AR089: 1, AR060: 1, AR033: 1, AR039: 1, AR104: 1 H0635: 2, S0418: 1, H0388: 1, H0436: 1 and S0031: 1.	AR096: 28, AR053: 10, AR039: 5, AR089: 5, AR052: 5, AR061: 3, AR055: 3, AR060: 2, AR033: 2, AR104: 2 S0007: 5, L0742: 5, L0731: 5, S0444: 4, L0769: 4, L0766: 4, L0740: 4, L0747: 4, L0749: 4, L0756: 4, L0596: 4, H0031: 3, L0065: 3, L075: 3, L0809: 3, S0126: 3, L0759: 3, S0354: 2, H0438: 2, H0083: 2, L0371: 2, L0770: 2,
·	1969 Thr-33 to Pro-39.	·
	6961	1970
	216 - 626	231 - 638
	564	565
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	HHAUZ72	HWMAM4 1
	554	555

	77-93	49-66
L0772: 2, L0803: 2, L0776: 2, L0783: 2, H0555: 2, L0439: 2, L0755: 2, L0758: 2, L0591: 2, S0011: 2, H0556: 1, H0685: 1, H0656: 1, H0349: 1, H0349: 1, H0135: 1, H0349: 1, H0646: 1, L0647: 1, L0794: 1, L0761: 1, L0777: 1, L0666: 1, L0663: 1, H0560: 1, L0663: 1, H0560: 1, L0663: 1, H0560: 1, L0663: 1, H0520: 1, H0560: 1, L0663: 1, H0520: 1, H0520: 1, R0521: 1, S0330: 1, H0521: 1, S0436: 1, L0777: 1, S0436: 1, H05436: 1, L0777: 1, S0436: 1, H05436: 1, L0777: 1, S0436: 1, H05436: 1, L0777: 1, L07	AR055: 15, AR060: 13, AR033: 12, AR089: 9, AR104: 8, AR052: 8, AR061: 7, AR096: 7, AR039: 7, AR053: 6	AR052: 6, AR096: 4, AR053: .4, AR060: 3,
	Ser-9 to Arg-15.	
	- 1971	1972
	9359	278 - 1690
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	858578	858584
	HCEOV70	HKGDL95
	556	557

	3-29, 33- 60, 76-98, 104-121
AR089: 3, AR033: 2, AR104: 2, AR061: 1, AR055: 1, AR039: 0 S0010: 3, L0731: 3, H0542: 2, S0134: 1, L0002: 1, S0418: 1, H0369: 1, H0486: 1, H0013: 1, S0280: 1, H0581: 1, S0049: 1, H0057: 1, S0022: 1, H0538: 1, H0529: 1, L0761: 1, L0667: 1, L0803: 1, L0653: 1, L0647: 1, L0793: 1, H0144: 1, L0355: 1, S0434: 1 and H0422: 1	AR055: 8, AR053: 6, AR104: 6, AR060: 6, AR033: 6, AR096: 5, AR052: 5, AR089: 4, AR061: 4, AR039: 3 L0748: 11, L0752: 5, S0003: 4, H0638: 3, L0747: 3, L0755: 3, L0759: 3, H0171: 2, T0114: 2, H0674: 2, S0422: 2, L0764: 2, L0766: 2, L0775: 2, L0740: 2, L0754: 2, L0749: 2, L0758: 2, H0170: 1, T0002: 1, H0295: 1, H0341: 1, S0212: 1, S0442: 1, S0444: 1, H0574: 1, H0156: 1,
	Asp-28 to Trp-33, Gly-59 to Ser-71.
	1973
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	00 20 22	33-86, 90- 115, 123-	147, 10- 30, 45-61										
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H0575: 1, H0596: 1, H0530: 1, L0157: 1, H0123: 1, H0620: 1, S0388: 1, H0428: 1, H0031: 1, H0264: 1, S0014: 1, S0450: 1, H0529: 1, L0763: 1, L0770: 1, L0655: 1, L0809: 1, S0052: 1, S0374: 1, H0520: 1, H0547: 1, S0122: 1, H0670: 1, H0648: 1, H0521: 1, S3014: 1, L0777: 1, H0670: 1, L0777: 1, H0670: 1, L0777: 1, H0670: 1, L0777: 1, H0646:	1, L0589: 1	AK104: 18, AK052: 17, AR033: 16, AR053: 9,	AR096: 8, AR089: 6, AR060: 5, AR039: 4,	AR061: 4,	S0414: 17 L0752: 13,	S0222: 11, L0439: 11	H0441: 8, F	8, L0777: 8, L0741: 7,	S0010: 6, H0327: 6, S0036:	6, L07/9: 6, H0620: 5,	n0031: 3, L0803: 3, 3 4. H0644: 4. L0805: 4	L0809: 4, L	4, H0599: 3, H0059: 3,
		Asn-30 to Cys-37.											
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L0768: 3, L0804: 3, L0774:	L0751: 3, L0754: 3, L0750:	3, S0412: 3, S0300: 2, H0438: 2, H0012: 2, S0050:	2, S0388: 2, T0010: 2,	H0615: 2, H0553: 2, L0769:	2, L0794: 2, L0776: 2,	L0789: 2, L0666: 2, L0663:	2, L0438: 2, L0743: 2,	L0753: 2, L0755: 2, L0759:	2, S0031: 2, S0260: 2,	L0608: 2, H0717: 1, H0716:	1, S6024: 1, S0282: 1,	L0005: 1, S0007: 1, S0220:	1, H0586: 1, H0333: 1,	H0013: 1, S0049: 1, H0050:	1, H0023: 1, H0399: 1,	H0688: 1, H0040: 1, T0067:	1, S0386: 1, H0100: 1,	S0039: 1, S0112: 1, L0351:	1, S0294: 1, S0440: 1,	L0763: 1, L0800: 1, L0764:	1, L0662: 1, L0775: 1,	L0651: 1, L0661: 1, L0807:	1, L0657: 1, L0793: 1,	L0664: 1, H0520: 1, H0547:	1, H0593: 1, H0689: 1,	H0670: 1, H0648: 1, H0696:	1, L0609: 1, L0747: 1,
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	103-122, 6-22	,						188-227,	269-293,	182-202,	50-72,	118-137,	153-170,	241-258,	14-30		99-126,	19-37, 70-	98					
L0756: 1, L0731: 1, S0434: 1 and S0021: 1.	AR055: 17, AR033: 9, AR061: 9, AR060: 8, AR052: 8 AR089: 6	5, AR096:	AR053: 5, AR039: 4	H0427: 1, H0575: 1, S0010:	1, H0390: 1, S0346: 1,	L0163: 1, S6028: 1, H0428:	1, S0150: 1 and L0743: 1.		AR096: 6, AR089: 4,	AR039: 4, AR104: 3,	AR055: 3, AR060: 3,	AR061: 3, AR033: 2	H0419: 3, S0282: 2,	S0028: 2, H0717: 1, H0381:	1, L0105: 1, H0135: 1,	S0052: 1 and S0044: 1.	AR039: 5, AR033: 4,		AR052: 3, AR089: 2,	AR055: 2, AR104: 2,	AR061: 2, AR053: 1	L0777: 4, L0751: 3,	L0747: 3, H0661: 2, L0648:	2, L0561: 2, L0779: 2,
								6 Trp-8 to Arg-14,	Asp-74 to Gln-79,	Ala-96 to Thr-104.							Asn-159 to Thr-173. AR039:							
	1975							1976	•	•							1977							
	817 - 1185					,		32 - 946									85 - 603							
	570							571									572							
	858727							858754									858877							
	HMIBL51							HFXJP30									HCHMP94							
	560							561									562							

	77-96
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L0753: 2, S0342: 1, H0484: 1, S0358: 1, L0009: 1, H0411: 1, S0222: 1, S6014: 1, H0546: 1, H0123: 1, H0484: 1, S0366: 1, H0413: 1, H0494: 1, S0344: 1, H0529: 1, L0769: 1, L0627: 1, L0774: 1, L0378: 1, L0776: 1, L0655: 1, L0663: 1, S0148: 1, S0380: 1, H0478: 1, L0743: 1, L0439: 1, L0750: 1 and S0196: 1.	8: 0: 22: 36: 24:
	Met-1 to Ser-8, Gln-37 to Asn-42, Lys-47 to Glu-54, Glu-61 to Gly-69.
	1978
	76 - 378
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	89-106, 126-142, 56-72
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S0015: 1, H0538: 1, L0598: 1, L0772: 1, L0800: 1, L0662: 1, L0649: 1, L0775: 1, H0519: 1, H0593: 1, S3014: 1, S0032: 1, L0757: 1, S0434: 1, H0653: 1, H0667: 1, S0276: 1 and S0196: 1.	AR052: 12, AR055: 8, AR053: 6, AR063: 6, AR089: 6, AR061: 6, AR060: 5, AR096: 1, AR104: 1, AR039: 0 L0794: 5, L0766: 3, L0759: 3, S0212: 2, H0318: 2, L0803: 2, L0804: 2, L0378: 2, L0665: 2, L0438: 2, L0439: 2, L0599: 2, L0439: 2, L0439: 2, L0599: 2, L0599: 1, H0669: 1, S0346: 1, H0669: 1, S0358: 1, H0370: 1, H0056: 1, S032: 1, L0483: 1, H0050: 1, H0163: 1, H0553: 1, H0163: 1, H0569: 1, L0638: 1, L0646: 1, S0426: 1, H0529: 1, L0646: 1, S0426: 1, L0638: 1, L0646: 1, S0426: 1, L0638: 1, L0646: 1, S0426: 1, L0638: 1, L0646: 1, S0629: 1, L0638: 1, L0646: 1, S0629: 1, L0638: 1, L0646: 1, L0646: 1, L0638: 1, L0646: 1, L0648:
S0015: 1, H053; 1, L0772: 1, L06 L0662: 1, L064; 1, H0519: 1, H0 S3014: 1, S0033 1, S0434: 1, H0 H0665: 1, H066 1 and S0196: 1.	AR052: 12, AR055: AR065: AR083: AR089: 6, AR061: AR104: 1, AR039: L0794: 5, L0766: 3, L0759: 3, S0212: 2, L0378: 2, L0804: 2, L089: 2, L0378: 2, L0655: 2, L0591: 1, R0050: 1, R0373: H0050: 1, R0373: H0050: 1, R0116: 1, L0769: 1, L0638: 1, L0769: L0769: 1, L0638: 1, L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769: L0769:
	Asn-7 to Arg-15, His-143 to Phe-148.
	H 1979
	634 - 137
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	243-259, 71-87, 318-334
53: 90: d	0, 176: 176: 264: 136:
L0381: 1, L0375: 1, L0653: 1, L0659: 1, L0782: 1, L0809: 1, L0793: 1, H0691: 1, H0435: 1, H0659: 1, H0648: 1, S0152: 1, S0390: 1, S0027: 1, S0028: 1, L0777: 1, L0731: 1, S0260: 1, L0596: 1, S0192: 1 and S0424: 1.	Pro-54 to Tyr-61, AR055: 183, AR096: 110, Asp-132 to Leu-139, AR089: 21, AR060: 20, AR104: 18, AR039: 4, AR052: 4, AR053: 3 H0341: 2, S0045: 2, H0551: 2, H0556: 1, S0376: 1, H0619: 1, H0437: 1, H0619: 1, H0437: 1, H06009: 1, H0650: 1, H0645: 1, H0644: 1, H0383: 1, H0644: 1, H0383: 1, H0668: 1, H0383: 1, H0644: 1, H0436: 1, R0648: 1, H0645: 1, H0644: 1, H0645: 1, H0645: 1 and S0424: 1.
	Pro-54 to Tyr-61, Asp-132 to Leu-139, Ser-176 to Asp-183.
	1980
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VO 01/90304	PC1/US01/16450
144-160	
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1981 Arg-3 to Phe-10, Val-18 to Cys-23, His-64 to Tyr-73, Ser-181 to Gly-18 Glu-211 to Pro-22 Gly-284 to Ser-28 Thr-296 to Tyr-30 Phe-308 to Gly-31 Pro-321 to Asp-32	
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S0376: 1, H0580: 1, H0619:	1, H0411: 1, H0409: 1,	H0586: 1, H0587: 1, H0574:	: 1, H0486: 1,	T0039: 1, T0040: 1, T0109:	: 1, T0082: 1,	H0421: 1, H0194: 1, H0231:	: 1, H0046: 1,	H0024: 1, H0014: 1, H0051:	: 1, S6028: 1,	H0553: 1, H0628: 1, L0055:	: 1, H0212: 1,	H0124: 1, H0598: 1, H0038:	l, H0634: 1, H0268: 1,	H0412: 1, H0056: 1, H0494:	: 1, H0641: 1,	, S0142: 1, S02	1, S0426: 1, H0529: 1,	, L0372: 1, L06	l, L0374: 1, L0764: 1,	.0768: 1, L0794: 1, L0803:	I, L0805: 1, L0652: 1,	, L0664: 1, SOC	1, H0519: 1, H0670: 1,	H0672: 1, H0539: 1, L0602:	1, S0350: 1, S3012: 1,	, S0032: 1, L07	1, L0751: 1, L0779: 1,	.0753: 1, L0757: 1, S0434:	1, L0581: 1, L0593: 1,
S0376: 1	1, H0411	H0586: 1	1, L0622	T0039: 1	1, L0021	H0421: 1	1, H0544	H0024: 1	1, T0010	H0553: 1	1, H0383	H0124: 1	1, H0634	H0412: 1	1, H0625	H0633: 1	1, S0426	L0369: 1	1, L0374	L0768: 1	1, L0805	L0783: 1	1, H0519	H0672: 1	1, S0350	S0037: 1	1, L0751	L0753: 1	1, L0581
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<u> </u>	Arg-9 to Lys-26, Pro-79 to Asp-87.	<u>6</u>		7			4		7		2		_0			<u> </u>								- <b></b>		<u>. P</u>
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1, L0800: 1, L0768: 1, L0766: 1, L0386: 1, L0775: 1, L4501: 1, L0665: 1, H0519: 1, H0648: 1, H0521: 1, S0406: 1, H0576: 1, L0749: 1, L0779: 1, L0780: 1, L0752: 1, L0731: 1, L0757: 1, L0758: 1, L0591: 1, H0423: 1 and H0422: 1.	AR053: 8, AR104: 8, AR055: 4, AR061: 3, AR089: 2, AR039: 2, AR060: 2, AR052: 2, AR053: 1, AR096: 1 L0758: 4, L0769: 3, L0803: 3, H0295: 2, S0007: 2, L0438: 2, L0740: 2, L0757: 2, S0418: 1, S0420: 1, L0021: 1, H0706: 1, H0052: 1, S0250: 1, H0328: 1, H0213: 1, S0366: 1, L0662: 1, L0774: 1, L0659: 1, L0790: 1, L064: 1, S0027: 1, L0741: 1, L0743: 1, L0756: 1, L0777: 1 and L0731: 1.	AR096: 1, AR033: 1, AR061: 1, AR055: 0, AR060: 0, AR089: 0,
		Val-2 to Arg-12, His-21 to Ile-43.
	1983	1984
	341 - 3	351 - 689
	578	579
	859028	859036
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	568	695

		352-378,	232-252,	307-324,	271-287																	1-28, 184-	201, 157-	173		
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		Met-1 to Gly-6,	Arg-8 to Ala-19,	Ser-32 to Ala-46,	Ala-57 to Pro-76,	Ala-78 to Arg-88,	Thr-95 to Ser-104,	Lys-126 to Glu-138.														Gln-40 to Glu-45,	Glu-96 to Glu-102,	Asn-256 to Thr-266,	Lys-311 to Ser-322.	
		1985																				1986		-		
		118-	1341		_																	108	1124			
		580																				581				
		859165																				829189				
	٧.	HHFKC41																				HMWGG4	4			
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L0752: 8, L0748: 12, L0752: 8, L0744: 7, H0124: 6, L0770: 6, H0733: 5,	5, L0766: 5, L0804: 5, L0805: 5, L0776: 5, L0740: 5, L0745: 5, L0750: 5,	L0777: 5, L0809: 4, S0442: 3, H0032: 3, L0774: 3, L0742: 3, L0757: 3, L0759:	3, S0436: 3, S0114: 2, S0360: 2, S0222: 2, L0622: 2, H0545: 2, H0673: 2,	L0598: 2, L0794: 2, L0775: 2, L0375: 2, L0651: 2,	L0659: 2, L0526: 2, L0783: 2, L0528: 2, H0547: 2, 80126: 2, S0330: 2, S0380:	2, H0696; 2, S0188; 2, L0751; 2, L0747; 2, L0755;	2, L0605: 2, H0624: 1, H0265: 1, S0040: 1, S0218:	1, H0630: 1, H0541: 1, H0638: 1, H0580: 1, H0728: 1 H0734: 1, S0476: 1	S6014: 1, H0610: 1, H0486: 1, L0586: 1, T0060: 1.	H0575: 1, T0082: 1, H0004: 1, H0581: 1, H0087: 1, H0014: 1, H0083: 1, H0188:
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	15-41, 41- 63, 86-109
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1, H0687: 1, S0003: 1, H0328: 1, T0023: 1, L0055: 1, H0165: 1, S0364: 1, S0366: 1, S0366: 1, L0564: 1, H0494: 1, L0475: 1, S0016: 1, H0560: 1, S0294: 1, S0438: 1, S0440: 1, H0509: 1, H0131: 1, S0150: 1, H0641: 1, S0422: 1, S0002: 1, L0520: 1, L0371: 1, L0796: 1, L0648: 1, L0761: 1, L0648: 1, L0521: 1, L0648: 1, L0384: 1, L0530: 1, L0787: 1, L0788: 1, S0053: 1, S0148: 1, H0689: 1, H0659: 1, S0378: 1, S0152: 1, H0522: 1, H0704: 1, S0044: 1, H0478: 1, H0707: 1, S3014: 1, L0731: 1, L0758: 1, S0031: 1, S0434: 1 and S0276: 1.	- 1987 Tyr-10 to Asp-15, AR096: 2, AR104: 2, Asp-64 to Gly-72, AR055: 1, AR089: 1, Gln-74 to Lys-85, AR060: 1, AR033: 0, Gly-110 to Arg-122. AR061: 0, AR052: 0 S0126: 4, H0271: 1, H0164: 1, S0028: 1 and
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·	572 HOEMM2 859190 3

	48-65, 121-137, 73-89	51-73
		103050, 103050, 124030, 124030, 138981, 182380, 188826, 190040, 190040,
		22q13.1
S0260: 1.	AR052: 4, AR055: 3, AR053: 3, AR060: 2, AR033: 2, AR089: 2, AR104: 1, AR096: 1, AR104: 1, AR039: 0 S0126: 3, H0658: 3, H0556: 2, H0576: 2, L0600: 2, H0265: 1, S0360: 1, H0592: 1, H0051: 1, H0031: 1, H0135: 1, H0652: 1, L0641: 1, L0803: 1, L0375: 1, L0666: 1, H0547: 1, S0031: 1 and S0026: 1.	AR033: 13, AR052: 6, AR104: 5, AR060: 4, AR055: 4, AR061: 4, AR053: 3, AR089: 3, AR096: 2, AR039: 1 L0748: 7, L0747: 6, L0805: 5, L0803: 4, L0776: 4, L0439: 4, L0757: 4, H0549: 3, L0794: 3, L0809: 3, L0750: 3, L0777: 3, H0624: 2, H0635: 2, H0012: 2, L0775: 2, L0744: 2, L0731: 2, S0276: 2, H0556: 1, S0114: 1, H0650: 1, H0255: 1, S0360: 1, L0394:
	Thr-116 to Gly-122, Lys-142 to Pro-150, Pro-164 to Ala-172, Glu-184 to Asn-189.	Glu-9 to Gly-14, Gln-75 to Val-81, Ser-94 to Gly-116.
	1988	1989
	31 - 873	775 -
	583	584
	859200	859201
	HTXPN78	HFPGR87
	573	574

VO 01/90304	PC1/US01/10450
	252-280, 319-342, 202-222, 157-173, 385-401, 174-190
1, \$0222: 1, H0441: 1, H0392: 1, H0333: 1, \$0474: 1, H0052: 1, H0194: 1, H0235: 1, H0597: 1, H0231: 1, H0546: 1, H0150: 1, H0620: 1, H0328: 1, H0615: 1, H0674: 1, H0168: 1, H0135: 1, H0163: 1, L0497: 1, L0804: 1, L0661: 1, L0543: 1, L0791: 1, L5286: 1, H0144: 1, \$0126: 1, H0144: 1, \$0126: 1, H0696: 1, L0743: 1, L0749: 1, L0780: 1, L0752: 1, L0758: 1, \$0031: 1, L0591: 1 and 1,0608: 1	AR052: 8, AR055: 8, AR053: 6, AR096: 6, AR089: 5, AR060: 4, AR033: 4, AR039: 4, AR061: 3, AR104: 3 L0758: 4, S0358: 3, L0766: 3, H0038: 2, L0748: 2, L0754: 2, L0756: 2, L0759: 2, H0265: 1, H0223: 1, H0222: 1, H0159: 1, L0002: 1, S0116: 1, H0586: 1, T0040: 1, H0013: 1, H0052: 1, T0110: 1, L0157: 1, H0050: 1, H0266: 1, S0250: 1, S0364: 1, H0616:
·	Pro-12 to Lys-33, Asn-41 to His-46, Pro-48 to Ser-58, Gly-71 to Asp-78, Ala-94 to Gly-102, Ser-133 to Ser-140, Arg-197 to Lys-202.
	1990
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	727-762, 5-21, 556- 572
1, H0264: 1, H0509: 1, H0641: 1, L0646: 1, L0773: 1, L0662: 1, L0776: 1, L0655: 1, L0659: 1, L0809: 1, L0666: 1, L0664: 1, S0126: 1, S0380: 1, H0521: 1, L0779: 1, L0593: 1, S0242: 1 and L0697: 1.	Arg-105 to Cys-111, AR069: 5, AR052: 2, Arg-105 to Cys-111, AR069: 2, AR096: 2, AR096: 2, Leu-152 to Glu-158, AR039: 1, AR061: 1, Tyr-213 to Pro-223, AR104: 0, AR053: 0 Ala-246 to Asp-256, S0192: 18, H0521: 7, Leu-274 to Cys-283, L0659: 6, S0126: 6, L0744: Glu-297 to Tyr-302, 6, H0486: 5, L0666: 5, Pro-322 to Leu-327, S0022: 4, L0438: 4, L0754: Asp-333 to Val-343, 4, S0194: 4, S0045: 3, Thr-490 to Lys-496, H0662: 2, S0132: 2, S0476: Pro-531 to Asp-541, 2, H0392: 2, H0661: 2, Arg-545 to Gly-551, H0575: 2, H0581: 2, S0250: Asp-683 to Thr-713: H0622: 2, H0591: 2, H0551: 2, H0622: 2, L0771: 2, H0663: 2, L0664: 2, L0665: 2, H0144: 2, S0027: 2, S0022: 2, S0028: 2, L0664: 2, L0665: 2, H0144: 2, S0027: 2, S0028: 2, S0027: 2, S0027: 2, S0027: 2, S0028: 2, S0027: 2, S0028: 2, S0027: 2, S0022: 2, S0027: 2, S0028: 2, S0027: 2, S0027: 2, S0027: 2, S0028: 2, S0027: 2, S0027: 2, S0028: 2, S0027: 2,
	35 - 2344
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S0206: 2, L0740: 2, L0751: 2, H0595: 2, L0596: 2, H0506: 2, H0170: 1, T0049: 1, S0212: 1, H0638: 1, S0420: 1, S0442: 1, S0468: 1, S0468: 1, H0369: 1, H0592:	1, H0586: 1, S0010: 1, H0705: 1, H0310: 1, H0046: 1, T0010: 1, H0375: 1, H0266: 1, H0687: 1, S0214: 1, H0039: 1, L0483: 1, H0030: 1, H0031: 1, H0032: 1, S0366: 1, H0598: 1, H0038: 1, H0380: 1, H0268:	1, H0413: 1, H0056: 1, S0440: 1, H0652: 1, S0142: 1, S0344: 1, L0770: 1, L0638: 1, L0646: 1, L0649: 1, L0381: 1, L0806: 1, L0657: 1, L0658: 1, L0518: 1, L0809: 1, L0789: 1, H0682: 1, S0332: 1, H0696: 1, S0404: 1, S0406: 1,	H0555: 1, H0627: 1, S0037: 1, S3014: 1, L0747: 1, L0755: 1, L0757: 1, L0588: 1, L0591: 1, S0026: 1, H0653: 1, H0665: 1 and S0196: 1.
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	62-94	143-176, 66-93, 22- 50, 106- 125
L0779: 1, L0777: 1, L0755: 1, L0592: 1, L0599: 1, S0194: 1, S0276: 1, H0543: 1, S0424: 1 and H0506: 1.	AR052: 1, AR104: 1, AR089: 1, AR061: 1, AR055: 1, AR039: 0, AR033: 0, AR096: 0, AR060: 0, AR053: 0 S0250: 1 and H0547: 1.	AR053: 2, AR096: 1, AR055: 1, AR033: 1, AR061: 1, AR089: 0, AR060: 0, AR104: 0, AR052: 0 H0046: 20, H0529: 3, L0439: 3, H0624: 2, H0038: 2, H0547: 2, L0588: 2, H0556: 1, H0484: 1, H0450: 1, H0619: 1, H0549: 1, H0550: 1, H0497: 1, T0040: 1, H0013: 1, H0599: 1, H0052: 1, H0509: 1, H0538: 1, L0654: 1, H0520: 1, H0551: 1, R0509: 1, H0551: 1, R0509: 1, H0551: 1, R0509: 1, H0551: 1, H0520: 1,
		Cys-179 to Ser-189, Ala-216 to Tyr-223.
	1993	1994
	13 - 318	198 - 875
	588	685
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	33-70, 78-	99, 7-24,	5/-/3,	117-133												· · · · · · · · · · · · · · · · · · ·								153-169			
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1, L0592: 1, L0593: 1, L0595: 1 and H0506: 1.	AR055: 11, AR053: 10,		AR060: 7, AR089: 6,	AR033: 6, AR061: 5,	AR039: 5, AR104: 3	H0521: 7, L0748: 4,	H0656: 3, H0586: 2, H0264:	2, L0740: 2, S0436: 2,	H0542: 2, H0171: 1, T0002:	1, H0222: 1, S0040: 1,	H0294: 1, S0134: 1, H0583:	1, S0212: 1, S0356: 1,	S0045: 1, H0069: 1, H0318:	1, H0421: 1, H0052: 1,	H0081: 1, H0050: 1, H0284:	1, H0428: 1, S0036: 1,	H0551: 1, H0494: 1, S0144:	1, S0344: 1, L0807: 1,	L0790: 1, H0547: 1, H0435:	1, H0539: 1, S0152: 1,	S0028: 1, S0032: 1, L0750:	1, L0777: 1, L0759: 1,	H0445: 1 and H0422: 1.	AR096: 5, AR089: 4,	-	AR052: 1, AR061: 1,	AR104: 0, AR053: 0
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	74-97, 3- 19	55-81, 36- 52, 84-100
	I	188826, 250100, 250800, 250800
		22q13.2- q13.31
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	Pro-30 to Arg-35, Glu-41 to Glu-51, Ser-54 to Trp-62, Gly-69 to Trp-77.	Pro-10 to Arg-15.
	1997	1998
	45 - 485	389 - 745
	592	593
	859769	859792
	НТРДМ61	НТРОН87
	582	583

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L0773: 2, 2, L0809: H0341: 1, 1, S0360: H0550: 1, 1, H0673: H0413: 1, 1, H0661: 1, H0690: H0521: 1, L0759: L0366: 1, L0366: 1,	S0424: 1.  AR053: AR053: AR033: AR060: AR104: L0745: 7 L0768: 2, 2, L0542: H0672: 2, 2, L058: T0049: 1, 1, S0358: H0580: 1, H0580: 1,
	Leu-10 to Ser-20, Ala-49 to Gly-55, Ala-69 to Ala-74.
	1999
	284 - 760
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	859796
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	86-102, 54-70
L0021: 1, H0251: 1, H0266: 1, S0003: 1, S0214: 1, H0428: 1, H0535: 1, H0644: 1, H0674: 1, H0598: 1, H0674: 1, H0616: 1, H0268: 1, H0509: 1, S0002: 1, L0371: 1, L0770: 1, L0652: 1, L0523: 1, L0562: 1, L0523: 1, L0563: 1, S0126: 1, H0435: 1, H0670: 1, H0539: 1, S0380: 1, H0522: 1, S0044: 1, H0345: 1, L0750: 1, L0750: 1, L0750: 1, L0750: 1, H0445: 1 and L0603: 1.	
	Arg-7 to Ala-14, Phe-113 to Arg-118, Pro-124 to His-129, Glu-145 to Ala-153.
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3, H0449: 2, S0358: 2, S0376: 2, S0444: 2, H0392: 2, T0006: 2, H0477: 2, L0775: 2, L0806: 2, S0152:	2, H0436: 2, L0751: 2, L0750: 2, L0758: 2, S0436: 2, H0423: 2, H0624: 1, H0556: 1, H0157: 1, H0295:	1, H0294: 1, S0114: 1, H0657: 1, H0656: 1, H0484: 1, H0483: 1, S0356: 1, S0360: 1, S0408: 1, H0637:	1, 50007: 1, 50045: 1, H0391: 1, H0586: 1, H0497: 1, H0331: 1, H0485: 1, T0109: 1, T0048: 1, S0474:	1, E0040. 1, 110040. 1, S0051: 1, H0083: 1, H0606. 1, H0169: 1, H0316: 1, H0268: 1, H0412: 1, H0413: 1, T0042: 1, S0464: 1, H0633: 1, 10763: 1, 10770.	1, L0769: 1, L0638: 1, L0771: 1, L0648: 1, L5564: 1, L0381: 1, L0774: 1, L0378: 1, L0655: 1, L0659:	1, L0809: 1, L0788: 1, L0532: 1, H0682: 1, H0659: 1, S0328: 1, S0380: 1, S0350: 1, H0696: 1, S0406:

	383-406, 124-149, 8-35, 281- 302, 349- 368, 151- 171, 85- 104, 44- 62, 227-	245, 324 340, 29- 45, 189- 205	65-84, 302-318, 571-587, 130-146, 366-382, 492-508
			300037, 300076, 300123, 301201, 301845, 301900, 307340, 307700, 308000, 308000,
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			Ser-27 to Pro-35, Thr-87 to Ile-99, Pro-106 to Lys-112, Glu-119 to Ser-130, Ser-182 to Val-187, Lys-194 to Tyr-204, Lys-295 to Val-300, Lys-384 to Glu-390, Thr-512 to Thr-526, Ser-530 to Glu-556, Gln-556 to Lys-562,
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	859848		859875
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308240, 309555, 310490, 312000, 313350, 313850	109270, 109270, 109270, 109270, 115660, 120150, 120150, 148065, 148080, 148500, 150200, 154275, 162100, 170500, 170500,	171190, 176960, 182452, 185800, 221820,
	17q22-q24	
	AR061: 14, AR052: 5, AR055: 3, AR033: 2, AR089: 2, AR060: 1, AR053: 1, AR096: 0, AR039: 0, AR104: 0 H0144: 1 and L0755: 1.	
	Ser-49 to Ser-66,  Asp-152 to Lys-160,  Gly-186 to Asn-192,  Arg-200 to Ser-205,  Pro-223 to His-229,  Gly-240 to Thr-250.	
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	71-88	51-68, 4-21
230200, 249000, 253250, 600525, 600852,		
	AR089: 15, AR096: 15, AR052: 14, AR053: 12, AR060: 12, AR055: 11, AR104: 11, AR039: 10, AR033: 9, AR061: 6 H0171: 2, H0624: 1, S0222: 1, H0271: 1, S0390: 1, S0028: 1, L0786: 1 and S0031: 1.	AR039: 9, AR096: 8, AR053: 8, AR089: 7, AR052: 6, AR033: 5, AR055: 4, AR104: 4, AR060: 4, AR104: 2, L0766: 6, L0770: 3, H0632: 2, H0013: 2, L0483: 2, L0775: 2, L0663: 2, H0521: 2, L0759: 2, L0362: 2, S0354: 1, S0358: 1, H0486: 1, H0003: 1, H0318: 1, H0544: 1, H0457: 1, H0510: 1, H0428: 1, L0371: 1, L0521: 1, L0512: 1,
	Thr-26 to Lys-32, Asn-98 to Pro-105, Arg-133 to Thr-139.	Thr-33 to Thr-40, Lys-86 to Lys-103.
	2004	2005
	953 - 537	906 -
	599	600
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	43-64, 199-218, 119-135
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L0783: 1, L0664: 1, H0593: 1, H0365: 1, H0659: 1, H0658: 1, H0672: 1, S0378: 1, L0756: 1, L0758: 1, H0445: 1, L0480: 1 and L0599: 1.	AR055: 8, AR033: 6, AR060: 5, AR089: 5, AR104: 4, AR039: 4, AR052: 4, AR039: 4, AR061: 4, AR053: 4, AR061: 4, AR096: 4 H0618: 7, L0747: 6, L0439: 5, H0617: 3, L0766: 3, L0438: 3, H0580: 2, H0328: 2, L0783: 2, H0694: 2, S0434: 2, H0717: 1, S0442: 1, S0360: 1, S0408: 1, H0208: 1, S0045: 1, H0261: 1, H0550: 1, H0586: 1, H0333: 1, H0559: 1, H0024: 1, H0373: 1, H0399: 1, H0292: 1, H0135: 1, L5565: 1, L0761: 1, L0630: 1, L0767: 1, L0375: 1, L0653: 1, L0655: 1, L0807: 1, L0787: 1, H0547: 1, H0672: 1, H0576: 1, L0748: 1, L0787: 1, H0576: 1, L0748:
L0783: 1, 1, H0365: H0658: 1, 1, L0756: H0445: 1, L0599: 1.	AR055: AR060: AR104: AR052: AR061: H0618: L0439: 5 3, L0438: 2 2, S0434 S0442: 1 1, H0208: 1 1, H0246: 1 1, H0246: 1 1, H0292 L5565: 1 1, L0767 L0653: 1 1, L0767 H0672: 1 1, L0787
	Met-1 to Trp-10, Gln-12 to Thr-37.
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L0759: 1, S0011: 1 and	_		AR033: 5, AR061: 5,			AR053: 3, AR104: 0	S0053: 2	AR039: 38, AR033: 23,	R096: 21, AR104: 20	R052: 18, AR089: 17	AR053: 15, AR061: 14,	AR055: 14, AR060: 13	H0581: 3, H0522: 3,	.0747: 3, H0662: 2, H0553:	2, H0641: 2, S0053: 2,	H0689: 2, H0521: 2, L0748:	2, L.0731: 2, L.0759: 2,	H0543: 2, H0294: 1, H0657:	l, H0656: 1, S0418: 1,	S0358: 1, H0208: 1, H0619:	l, H0586: 1, H0587: 1,	H0427: 1, H0599: 1, H0575:	1, H0052: 1, H0545: 1,	H0009: 1, H0081: 1, H0510:	1, H0266: 1, H0212: 1,	H0211: 1, H0090: 1, H0100:	1, T0042: 1, H0494: 1,	H0646: 1, L0770: 1, L0659:
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·	88-105, · 35-51	36-56	174-190, 7-23, 70- 86
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	2009 Met-1 to Arg-6, Pro-24 to Ile-30.	Ser-13 to His-18, Phe-90 to Asp-100, Ser-118 to Thr-143.	Gln-96 to Glu-102, Asn-108 to Val-113, Gly-154 to Tyr-159.
	2009	2010	2011
	222 - 566	183 - 662	929 - 68
	604	605	909
	860167	860381	860461
	HWLEL47	HNGJG75	HKAJU40
	594	595	596

W O 01/90304	2 3 7 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	57-86, 20- 43, 127- 145
1, S0364: 1, H0494: 1, S0440: 1, H0509: 1, H0633: 1, S0144: 1, H0529: 1, L0372: 1, L0766: 1, S0126: 1, L0602: 1, S0152: 1, H0576: 1, L0779: 1, H0665: 1 and H0216: 1.	AR089: 3, AR033: 2, AR096: 2, AR039: 2, AR096: 2, AR039: 2, AR055: 0, AR051: 1, AR055: 0, AR054: 0, AR104: 0  L0754: 5, L0744: 4, L0659: 3, L0774: 3, S6024: 2, H0661: 2, H0645: 2, L0794: 2, L0766: 2, L078: 2, L0766: 2, L078: 2, L0766: 2, L078: 2, L0759: 2, L0766: 2, L078: 2, L0759: 1, H058: 1, H058: 1, H0575: 1, H041: 1, H058: 1, H0575: 1, H0590: 1, H0510: 1, H0050: 1, L0163: 1, H0050: 1, H0133: 1, H0590: 1, H0590: 1, H0590: 1, H0644: 1, H0050: 1, H0133: 1, H0551: 1, H0030: 1, H0135: 1, H0551: 1, H0030: 1, H0135: 1, H0551: 1, H0030: 1, H0509: 1, H0566: 1, H0566: 1, H0646: 1, H0650: 1, H0644: 1, H0630: 1, H0135: 1, H0551: 1, H0030: 1, H0135: 1, H0551: 1, H0030: 1, H0560: 1, H0560: 1, H0560: 1, H0560: 1, H0560: 1, H0560: 1, H0647: 1, H0660: 1, H0560: 1, H0660: 1, H066
	Val-43 to Gly-48, A A Leu-118 to Leu-128. A A A A A A A A A A A A A A A A A A A
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	72-89
1, S0344: 1, S0426: 1, L0598: 1, H0529: 1, L0762: 1, L0796: 1, L0372: 1, L0804: 1, L0774: 1, L0805: 1, L0656: 1, L0809: 1, L0666: 1, L0438: 1, H0547: 1, H0519: 1, H0683: 1, H0435: 1, H0659: 1, H0660: 1, H0696: 1, S0028: 1, L0742: 1, L0745: 1, L0746: 1, L0752: 1, L0757: 1, L0480: 1, L0591: 1, H0653: 1, S0192: 1, H0423: 1 and H0422: 1.	AR060: 2, AR053: 1, AR051: 1, AR033: 0, AR055: 0, AR096: 0, AR039: 0 H0144: 3, S0007: 2, H0550: 2, H0494: 2, L0794: 2, L0633: 2, L0666: 2, L0665: 2, S0330: 2, H0478: 2, S0040: 1, H0661: 1, H0637: 1, H0549: 1, H0431: 1, S0280: 1, H0575: 1, H0051: 1, H0355: 1, H0594: 1, H0288: 1, L0483: 1, H0644: 1, H0038: 1, H0616: 1, H0509: 1, H0517: 1, L0662: 1, L0791: 1, L0663:
	Glu-6 to Glu-16.
	2013
	234 - 536
	809
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	598

	91-107	344-371, 169-200, 313-340, 275-302, 15-42, 146-167, 119-135, 1-17, 210- 227, 237- 253
03: 1, :: 1, H0711: 44: 1, :: 1, L0751: H0423: 1.	55: 2, 96: 1, 53: 1, 39: 0,	089: 24, 060: 14, 053: 13, 055: 10, 04: 5 62: 10, 18, L0659: 18, L0664: 15, L0664: 15, L0664: 15, L0756: 03: 4, L0756: 02: 3, 002: 3,
1, L0664: 1, H0703: 1, L0438: 1, H0547: 1, H0711: 1, H0518: 1, S0044: 1, H0214: 1, L0439: 1, L0751: 1, L0731: 1 and H0423: 1.	AR061: 2, AR055: 2, AR089: 1, AR096: 1, AR033: 1, AR053: 1, AR060: 1, AR039: 0, AR104: 0 S0052: 2 and H0393: 1	AR096: 31, AR089: 24, AR033: 14, AR060: 14, AR052: 13, AR053: 13, AR039: 13, AR055: 10, AR061: 6, AR104: 5 L0731: 27, L0662: 10, S0360: 8, L0666: 8, L0659: 7, L0758: 7, S0358: 6, S0003: 6, L0803: 6, L0748: 6, L0747: 6, L0779: 6, L0752: 6, S0132: 5, L0664: 5, L0744: 5, L0754: 5, S0040: 4, H0662: 4, H0411: 4, H0251: 4, H0597: 4, L0471: 4, H0024: 4, S0022: 4, L0809: 4, L0663: 4, L0439: 4, L0749: 4, L0756: 4, L0362: 4, L0002: 3,
	Pro-16 to Cys-28, Val-79 to Gly-84.	5 Tyr-42 to Gly-48, Ser-62 to Arg-83, Asp-137 to Pro-148, Ser-201 to Arg-207.
	2014	2015
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	599	009

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0250:		0126:		0255:		0486:		0483:		7764:		0044:		0603:		0664:		[0393:		[0331:		10635:		10253:		10050:		0252:	
H0600: 3, H0599: 3, S0250:	3, H0039: 3, H0622: 3,	H0616: 3, L0805: 3, S0126:	3, H0521: 3, L0759: 3,	H0170: 2, S0212: 2, H0255:	2, S0418: 2, L0717: 2,	S0222: 2, H0592: 2, H0486:	2, H0590: 2, H0196: 2,	H0231: 2, H0373: 2, L0483:	2, L0564: 2, S0002: 2,	L0772: 2, L0641: 2, L0764:	2, L0806: 2, L0776: 2,	L0384: 2, H0144: 2, S0044:	2, H0555: 2, H0595: 2,	L0592: 2, L0599: 2, L0603:	2, S0194: 2, H0624: 1,	S0001: 1, H0663: 1, H0664:	1, H0638: 1, S0376: 1,	H0637: 1, H0580: 1, F	1, H0437: 1, H0453: 1,	H0370: 1, H0586: 1, H0331:	1, H0574: 1, H0559: 1	H0485: 1, H0013: 1, H0635:	1, H0427: 1, H0118: 1,	H0575: 1, H0036: 1, F	1, L0105: 1, H0318: 1	H0234: 1, H0546: 1, H0050:	1, H0105: 1, S0388: 1	H0271: 1, S0318: 1, H0252:	1, H0428: 1, H0553: 1,
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80 80 80	66-93, 98- 125, 374- 405, 351- 371, 41- 58, 217- 235, 166- 182, 286- 302, 318-
H0644: 1 1, S0366: H0634: 1 1, H0100 T0041: 1, 1, H0646 1, L0763: 1, 1, L0379: 1, S0340: 1, 1, S0380: H0579: 1, 1, L0750: 1, 1, L0750: 1, 1, L0757: 1, 1, L0757: 1, 1, L0757: 1, 1, L0422	16 Thr-9 to Asn-16, AR033: 4, AR061: 4, Thr-59 to Trp-70, AR060: 2, AR104: 2, Pro-92 to His-97, AR089: 2, AR053: 1, Thr-345 to Gly-351, AR055: 1, AR039: 0, Tyr-409 to Pro-426, AR052: 0 Arg-433 to Val-466. H0556: 6, L0438: 6, L0758: 6, L0766: 5, L0666: 5, L0747: 5, L0805: 4,
	601 HE9PJ48 861223 611 131 - 2010

334, 187-	
4, L0779: 11: 3, 2, L0776: 3, L0776: 3, H0638: 9: 2, 2, H0553: 5: 2, 2, H0144: 5: 2, 2, L0599: 5: 1, 1, T0049: 9: 1, 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599: 1, H0599:	4; 1, 4; 1, 1, H0063: 9: 1, 1, L0351: 5: 1,
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	62-80, 20- 39
S0440: 1, S0150: 1, H0633: 1, S0210: 1, H0529: 1, L0520: 1, L0763: 1, L0770: 1, L0761: 1, L0764: 1, L0764: 1, L0521: 1, L0646: 1, L0662: 1, L0775: 1, L0662: 1, L0775: 1, L0663: 1, L0663: 1, L0663: 1, L0663: 1, H0689: 1, H0684: 1, H0704: 1, S0406: 1, H0704: 1, S0406: 1, L0751: 1, L0752: 1, L0752: 1, L0751: 1, L0752: 1, L0753: 1, L0753: 1, L0753: 1, L0753: 1, L0753: 1, L0754: 1, L0751: 1, H0216: 1 and S0424: 1, L0751: 1, H0216: 1 and S0424: 1, L0752: 1, H0665: 1, H0136: 1, H0216: 1 and S0424: 1, L0752: 1, L0754: 1, L0751:	AR055: 11, AR033: 9, AR089: 7, AR060: 6, AR104: 6, AR052: 5, AR096: 5, AR053: 5, AR061: 5, AR039: 4 L0439: 4, L0754: 3, L0758: 3, L0809: 2, L0666: 2, L0438: 2, L0757: 2, S0358: 1, S0376: 1, S0360: 1, H0730: 1, H0351: 1, H0411: 1, S0222: 1, T0039: 1, H0581: 1, H0545: 1,
	Gly-88 to Ser-94, Glu-98 to Tyr-110.
	2017
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WO 01/90304	FC1/US01/1045
	52-75, 31-
	114835, 132700, 172490, 600968
	16q12-q13
H0050: 1, S0318: 1, S0334: 1, H0032: 1, L0351: 1, L0763: 1, L0770: 1, L0774: 1, L0775: 1, L0659: 1, L0779: 1, L0777: 1, L0755: 1, H0444: 1, S0436: 1 and S0196: 1.	AR096: 3, AR039: 3, AR053: 1, AR052: 1, AR033: 1, AR061: 1, AR089: 1, AR060: 0, AR055: 0 L0754: 12, L0748: 11, H0521: 9, L0770: 5, L0740: 5, L0747: 5, L0756: 5, L0766: 4, H0591: 3, S0002: 3, L0744: 3, H0457: 2, H0428: 2, H0690: 2, L0523: 2, L0654: 2, L0659: 2, L0438: 2, H0435: 2, L0439: 2, H0445: 2, L0599: 2, S0026: 2, H0542: 2, H0556: 1, H0421: 1, H0596: 1, H0586: 1, H0013: 1, S0280: 1, H0421: 1, H0596: 1, H0628: 1, L0055: 1, H0083: 1, H0266: 1, H0553: 1, H0628: 1, L0761: 1,
·	Thr-89 to Gly-97, Ser-100 to Thr-108.
	2018
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	HDPUM54
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	95-112, 38-54
L0803:   1,   1,   1,   1,   1,   1,   1,   1	, , , , , , , , , , , , , , , , , , ,
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L0771: 1, L0768: 1, L0803: 1, L0774: 1, L0776: 1, L0655: 1, L0790: 1, L0792: 1, L0666: 1, H0144: 1, H0670: 1, H0518: 1, H0579: 1, L0749: 1, L0779: 1, L0755: 1, L0758: 1, L0759: 1, L0596: 1, S0192: 1, S0194: 1 and S0276: 1.	AR089: 8, AR055: 7, AR060: 6, AR052: 6, AR033: 6, AR061: 5, AR039: 3, AR104: 3 L0779: 9, L0483: 6, L0748: 6, H0556: 5, H0264: 5, L0766: 5, L0740: 5, L0750: 5, L0769: 4, L0659: 4, L0663: 4, L0754: 4, L0758: 4, L0593: 4, S0114: 3, H0652: 3, H0673: 3, H0436: 3, L0747: 3, L0777: 3, L0731: 3, H0445: 3, L0596: 3, L0718: 3, H0402: 2, S0280: 2, H0619: 2, H0393: 2, S0280: 2, H0624: 2, H0271: 2, H0135: 2, L0637: 2, L0768: 2, L0794: 2, L0561:
	Ala-24 to Arg-29, Arg-82 to Gln-89.
	2019
	717 - 1103
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/O 01/90304 /,	101/0501/1010
	118-139, 151-167, 93-110, 63-79, 35- 51
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1, L0761: 1, L0764: 1, L0662: 1, L0375: 1, L0806: 1, L0776: 1, L0518: 1, L0809: 1, L0788: 1, L0790: 1, L0666: 1, L0665: 1, S0052: 1, S0374: 1, L0438: 1, H0519: 1, H0593: 1, H0689: 1, H0659: 1, H0660: 1, R0689: 1, H0659: 1, H0539: 1, H0576: 1, S0432: 1, H0345: 1, S3012: 1, S0390: 1, S3014: 1, S0027: 1, L0744: 1, L0780: 1, L0759: 1, L0589: 1, L0599: 1, H0667: 1, S0276: 1, H0543: 1, H0423: 1, S0458: 1, UNKWN: 1 and	AR053: 1, AR060: 1, AR104: 1, AR089: 1, AR055: 1, AR033: 0, AR061: 0, AR096: 0, AR039: 0, AR052: 0 L0766: 6, L0748: 6, L0740: 6, L0776: 4, H0521: 3, S0358: 2, H0266: 2, S0003: 2, S0344: 2, L0638: 2, L0805: 2, L0438: 2, S0380: 2, L0754: 2, L0747:
	51 - 563 2020
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	605 HMCHK65

WO 01/90304	FC1/0501/10450
	171-188
2, L0752: 2, L0755: 2, L0362: 2, H0624: 1, L0005: 1, H0580: 1, S0045: 1, S0046: 1, H0575: 1, S0010: 1, H0553: 1, H0269: 1, T0042: 1, S0150: 1, L0369: 1, L0770: 1, L0761: 1, L0794: 1, L0656: 1, L0787: 1, L0789: 1, L0665: 1, H0670: 1, H0660: 1, S0152: 1, L0439: 1, L0749: 1, L0779: 1, L0777: 1, L0759: 1, H0445: 1, H0343: 1, L0591: 1, S0192: 1 and H0543: 1.	AR033: 4, AR060: 3, AR096: 3, AR089: 2, AR039: 1, AR053: 1, AR104: 1, AR061: 1, AR055: 1, AR052: 0 L0438: 7, L0740: 4, H0416: 3, L0803: 3, L0777: 3, S0005: 2, H0544: 2, H0271: 2, H0090: 2, H0038: 2, H0551: 2, S0440: 2, L0766: 2, L0809: 2, H0436: 2, L0748: 2, L0439: 2, L0754: 2, L0758: 2, L0366: 2, H0265: 1, H0556: 1, H0583: 1, H0656: 1, H0341:
	Ser-43 to Ala-48, Ser-72 to Leu-78, Ala-100 to Ala-107, Ser-109 to Ile-115, Arg-166 to Asn-171.
	2021
	1422 - 2093
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	861328
	HAIDK89
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	257-287, 173-200, 220-241, 88-108, 52-70, 202-218, 1-17, 138- 154	56-83, 86- 104
	180105, 222800	
	7q33	
1, S0360: 1, S0408: 1, S0132: 1, S0476: 1, H0550: 1, S0222: 1, H0632: 1, H0492: 1, H0013: 1, L0021: 1, H0599: 1, S0049: 1, H0123: 1, H0553: 1, H0622: 1, H0135: 1, H0040: 1, H0616: 1, H0135: 1, L0641: 1, L0642: 1, L0662: 1, L0663: 1, L0663: 1, L0663: 1, L0663: 1, L0663: 1, L0749: 1, L0780: 1, L0749: 1, L0780: 1, L0749: 1, L0780: 1, L0749: 1, L0780: 1, L0759: 1 and H0422: 1.	AR055: 9, AR033: 6, AR060: 5, AR061: 5, AR052: 4, AR089: 3, AR096: 3, AR053: 2, AR104: 1, AR039: 0 L0603: 4, H0031: 3, S0010: 2, T0010: 2, L0438: 2, H0038: 1, H0616: 1, H0264: 1, S0426: 1, H0539: 1 and L0439: 1.	AR089: 8, AR055: 6, AR060: 6, AR052: 4, AR061: 4, AR096: 3,
	Ser-25 to Gly-48, Phe-83 to Asp-91, Pro-110 to His-123, Lys-134 to Thr-139.	
	2022	2023
	1389 - 478	215 - 586
	617	618
	861361	861611
	нтонг.88	HMEKU54
	209	809

53: 3,	04: 0	4: 7,	: 4, L0751:	22: 3,	: 3, H0056:	52: 3,	2, S0444:	50: 2,	: 2, L0803:	48: 2,	: 2, S0146:	47: 2,	2, L0600:	40: 1,	: 1, S0410:	76: 1,	: 1, H0643:	13: 1,	: 1, H0575:	18: 1,	: 1, H0024:	71: 1,	: 1, H0615:	35: 1,	: 1, T0042:	41: 1,	: 1, L0639:	73: 1,	1, L0774:
AR033: 3, AR053:	AR039: 1, AR10	L0769: 7, L0754: 7,	H0657: 4, L0764:	4, S0408: 3, S0222: 3,	H0327::3, H0046: 3, H0056:	3, L0756: 3, L0752: 3,	S0282: 2, S0356: 2, S0444:	2, H0580: 2, H0250: 2,	H0622: 2, H0625: 2, L0803:	2, L0666: 2, H0648: 2,	H0672: 2, S0380:	2, L0745: 2, L0747: 2,	L0777: 2, L0731:	2, H0556: 1, H0740: 1,	H0305: 1, H0125:	1, H0637: 1, S047	H0393: 1, H0586: 1, H0643:	1, H0486: 1, H00	H0635: 1, H0599: 1, H0575:	1, S0346: 1, H0318: 1,	S0474: 1, H0052: 1, H0024:	1, H0266: 1, H0271: 1,	H0188: 1, H0286: 1, H0615:	1, H0124: 1, H0135: 1,	H0634: 1, H0264: 1, T0042:	[1, H0132: 1, H0641: ]	H0652: 1, S0422: 1, L0639:	1, L0771: 1, L0773: 1,	L0662: 1, L0766: 1, L0774:
		-																								-		-	
																	•											-	

	105-131	22-57, 59- 89, 204- 231, 1-20, 326-342
1, L0776: 1, L0655: 1, L0659: 1, L0809: 1, L0367: 1, H0547: 1, H0670: 1, H0521: 1, H0696: 1, S0404: 1, S0406: 1, L0748: 1, L0740: 1, L0749: 1, L0779: 1, L0755: 1, L0759: 1, S0434: 1, S0026: 1, H0653: 1, H0667: 1, S0242: 1, S0412: 1, H0506: 1 and: 1.	AR039: 51, AR104: 25, AR033: 23, AR096: 17, AR055: 17, AR053: 14, AR089: 14, AR052: 13, AR060: 12, AR061: 8 L0592: 3, H0592: 2, L0769: 2, L0657: 2, L0742: 2, L0749: 2, L0731: 2, L0758: 2, L0759: 2, S0010: 1, H0150: 1, H0009: 1, H0290: 1, H0644: 1, S0038: 1, H0494: 1, H0633: 1, L0771: 1, L0775: 1, L0776: 1, L0636: 1, L0809: 1,	AR096: 1, AR089: 1, AR060: 1, AR033: 1, AR055: 1, AR039: 1, AR061: 1, AR104: 0,
	Gly-35 to Arg-41, Lys-51 to Phe-62, Pro-89 to Gln-94.	Tyr-132 to Tyr-140, Cys-143 to Ser-154, Gly-252 to Thr-259, Glu-296 to Ala-302,
-	2024	2025
	619 613 - 1017	620 32 -
·	861620 6	861668 6
	HOQBR51	610 HAMGP34
	609	610

		78-94, 46-
·		
AR052: 0, AR053: 0 S0474: 22, H0556: 3, H0012: 3, H0521: 3, L0777: 3, H0638: 2, S0344: 2, L0769: 2, L0766: 2, L0803: 2, L0774: 2, L0375: 2, L0809: 2, L0748: 2, L0745: 2, L0747: 2, L0756: 2, L0779: 2, L0731: 2, H0484: 1, S0420: 1, H0722: 1, H0550: 1, H0592: 1, H0318: 1, H0081: 1, H0620: 1, H0673: 1, L0638: 1, L0764: 1, L0804: 1, L0775: 1, L0655: 1, L0493: 1, L0659: 1, L0783: 1, L4501: 1, L0657: 1, S0328: 1, H0518: 1, L0646: 1, L0438: 1, H0547: 1, S0328: 1, H0518: 1, L0746: 1, L0749: 1,	H0445: 1, S0436: 1 and H0542: 1.	AR104: 28, AR033: 17, AR089: 11, AR060: 10, AR096: 10, AR053: 9, AR052: 7, AR039: 7, AR055: 3, AR061: 2 L0731: 11, L0439: 10, L0752: 6, L0779: 5, H0046: 4, H0494: 4, L0770: 4,
Gln-311 to His-326, Pro-361 to Leu-368.		Arg-8 to Val-14, Tyr-25 to Arg-32, Cys-38 to Trp-44, His-70 to Ser-75, Glu-100 to Glu-106, Gly-117 to His-127, Gln-130 to Ser-136, Ser-167 to Ala-172,
		- 2026
		918
		621
		861683
		HHELG22
		611

																												•	
								<del></del>		-		<del></del>				- 1.2							-						
L0766: 4, L0774: 4, S0010:	3, S0036: 3, L0764: 3,	L0771: 3, L0803: 3, L0657:	3, L0748: 3, L0759: 3,	H0542: 3, H0657: 2, S0360:	2, H0009: 2, H0562: 2,	H0050: 2, L0363: 2, L0768:	2, L0550: 2, L0776: 2,	L0655: 2, L0659: 2, H0648:	2, L0740: 2, L0754: 2,	L0756: 2, L0758: 2, L0588:	2, H0136: 2, H0265: 1,	H0686: 1, S0116: 1, H0341:	1, H0638: 1, S0418: 1,	S0356: 1, S0358: 1, S0046:	1, S0222: 1, H0497: 1,	H0333: 1, H0486: 1, H0013:	1, H0427: 1, H0156: 1,	H0599: 1, H0581: 1, H0309:	1, H0327: 1, S0312: 1,	S0214: 1, L0055: 1, H0038:	1, H0634: 1, H0433: 1,	L0370: 1, S0438: 1, H0646:	1, S0002: 1, L0598: 1,	H0529: 1, L0451: 1, L0769:	1, L0639: 1, L0637: 1,	L5575: 1, L0630: 1, L0800:	I, L0662: 1, L0381: 1,	L0775: 1, L0651: 1, L0653:	I, L0661: 1, L0809: 1,
Pro-184 to Ile-197,			Arg-228 to Glu-245.																										
				_								_							-		·								
	_										-									_									
			-	-																								-	
																		····					· · · ·						

	6-38, 147- 176, 111- 137, 79-95
	·
L0532: 1, L0664: 1, L0665: 1, H0701: 1, S0122: 1, H0365: 1, H0539: 1, S0152: 1, L0777: 1, L0755: 1, L0757: 1, H0445: 1, S0436: 1, L0592: 1, L0608: 1, L0595: 1, L0362: 1, L0361: 1, S0026: 1, S0242: 1, H0422: 1 and S0424: 1.	AR052: 6, AR053: 5, AR096: 4, AR060: 3, AR033: 3, AR089: 3, AR039: 3, AR055: 3, AR061: 2, AR104: 2 L0731: 7, L0748: 5, L0730: 5, L0775: 4, H0521: 4, L0740: 4, L0766: 3, L0774: 3, L0747: 3, S0026: 3, H0069: 2, S0010: 2, S0474: 2, S0438: 2, L0771: 2, L0768: 2, L0649: 2, L0806: 2, L0653: 2, L0775: 2, L0663: 2, H0701: 2, H0522: 2, L0779: 2, L0755: 2, H0265: 1, R0713: 1, H0295: 1, S0212: 1, S0420: 1, S0444: 1, S0408: 1, H0393: 1, H0549: 1, H0613: 1, H0592: 1, H0331: 1,
	2027
	219 - 773
	622
	861707
	HDPTD75
	612

	4-31, 76- 93, 97-114
	102200, 106100, 131100, 131100, 131780, 147050, 153700,
	11913
H0250: 1, L0021: 1, H0706: 1, H0318: 1, H0263: 1, H0123: 1, L0471: 1, H0024: 1, H0510: 1, H0615: 1, H0031: 1, H0570: 1, H0615: 1, H0674: 1, S0366: 1, S0036: 1, S0036: 1, S0036: 1, S0036: 1, S0036: 1, L0770: 1, L0769: 1, L0764: 1, L0767: 1, L0769: 1, L0655: 1, L0767: 1, L0661: 1, L0658: 1, L0767: 1, L0661: 1, L0658: 1, L0384: 1, L0809: 1, S0052: 1, H0672: 1, S0378: 1, L0439: 1, L0749: 1, L0750: 1, L0759: 1, S0031: 1, H0595: 1, S0031: 1, H0659: 1, H0659: 1, H06423: 1, H0659: 1, H0650: 1.	AR055: 24, AR033: 18, AR053: 15, AR089: 13, AR052: 12, AR061: 8, AR060: 7, AR096: 5, AR039: 2, AR104: 2 H0201: 2, L0764: 2, L0748: 2, L0779: 2, L0759: 2, H0265: 1, H0402: 1,
	Ser-128 to Gln-133, Ser-144 to Thr-149.
	2028
	. 191 637
	623
	861985
	HTLIC39
	613